ON KETOSIS

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KETOSIS is a well-known complication of uncontrolled diabetes; it develops during fasting (either voluntary, or secondary to severe disease of the alimentary tract) and also whenever the diet contains large quantities of fat. It arises in cattle and sheep, generally in association with lactation, when it causes considerable economic loss to farmers. In all these circumstances there is a relative increase in fat metabolism or a decrease in carbohydrate metabolism. For many years medical students were taught that "fat burns in the flame of carbohydrate": when the carbohydrate flame was not sufficiently bright, fat was incompletely burnt and ketosis followed. Shaffer's classical paper (Shaffer 1921) was the epitome of this view. He wrote:

"Evidence is presented which appears to point to the conclusion that a molecular ratio (for the combustion of fat and carbohydrate) of 1:1, which corresponds to a respiratory quotient of 0·76 is the limit of the avoidance of excretion of acetone bodies. With quotients higher than 0·76 the catabolism of the antiketogenic glucose, or its equivalent from protein and glycerol, is great enough to remove acetoacetic acid as fast as it is formed."

The factors determining the appearance of ketosis are now known to be more complex than this. Several circumstances besides the ratio of fat to carbohydrate in the metabolic mixture may contribute to the onset of ketosis, though it never develops when carbohydrate metabolism predominates. Biochemists are now far too sophisticated to use the old flame analogy. Yet no one has so far succeeded in defining precisely the conditions of the enzymic mechanisms in cell metabolism that determine the presence of ketosis.

Methods and Normal Standards

The classical colour test for ketone bodies in the urine, first described by Rothera (1908), is performed thus: about 5 ml. of urine is placed in a test-tube, sufficient ammonium-sulphate crystals are added for saturation and the tube shaken; then one or two small crystals of sodium nitroprusside, or 2 or 3 drops of concentrated solution, are added; finally concentrated ammonia solution is poured slowly down the side. A positive result is indicated by the formation of a purple colour at the junction of the two liquids. The observation of this rich and beautiful colour is one of the attractions of research on ketosis. Nowadays the nitroprusside test is usually performed by adding a drop of urine to an 'Acetest' tablet. This is more convenient, but the purple formed on the tablet lacks the vividness present in solution. This colour is given by acetoacetic acid (CH_3COCH_2COOH) and acetone (CH_3COCH_3), but not by β-hydroxybutyric acid ($CH_3CHOHCH_2COOH$) which, of course, is not a chemical ketone. (Indeed, the terms "ketosis" and "ketone bodies" are chemical misnomers, but they are so well established that any attempt to change them would be futile.) The nitroprusside reaction cannot be the basis of a quantitative test, but it remains a useful qualitative guide to clinical ketosis.

For quantitative studies acetone, acetoacetate, and β-hydroxybutyrate must be estimated separately. There are several reliable methods for estimating acetone in biological material. Acetoacetate can easily be converted quantitatively into acetate by heat in the presence of sulphuric acid. β-hydroxybutyrate can be converted into acetone by oxidation (usually with bichromate) and treatment with acid. In the past it has been difficult to effect this oxidation quantitatively. This, however, can be brought about if *m*-phosphoric acid is used as a catalyst. Details of technique can be found elsewhere (Johnson et al. 1958). All the quantitative methods at present available for measuring ketosis are cumbersome and not specific. A quick and specific method for detecting and measuring β-hydroxybutyrate is badly needed: enzymic techniques may provide such a method.

There may be other ketone bodies in biological material. Thin and Robertson (1952) have shown that isopropanol contributes to bovine ketosis, though there is no evidence that this substance is formed in significant amounts in non-ruminants.

Acetoacetic acid is undoubtedly the primary ketone body. It is readily converted to acetone on standing; and acetone found in blood or urine may be a chemical artefact. Acetoacetate is reduced to β-hydroxybutyrate enzymatically in the tissues. This may be a detoxicating mechanism because β-hydroxybutyric acid is a weaker acid (pK 4·4) than acetoacetic acid (pK 3·8). Carbonic acid is weaker still, with a pK value of 6·1.

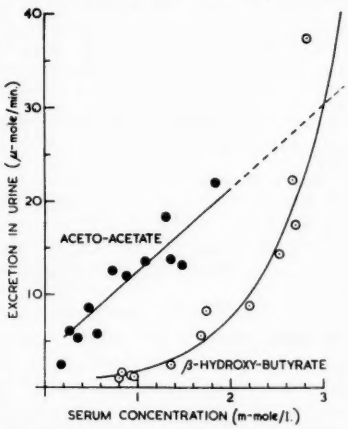

Fig. 1—Relation between rate of urinary excretion of ketone bodies and serum level during experimental ketosis in man (from experiments with R. E. Johnson).

In mild ketosis, acetoacetic acid is usually the predominant ketone body in both blood and urine, but in severe cases β-hydroxybutyric acid is the main component. The nitroprusside test is thus particularly unreliable in assessing changes in patients with severe ketosis.

The kidney treats the two acids differently (fig. 1). The relation between acetoacetate levels in the blood and the rate of urinary excretion is usually a straight line. On the other hand, β-hydroxybutyrate is treated by the kidney as a threshold substance. Little or none appears in the urine when ketosis is slight, but large amounts are present when the condition is severe.

TABLE I—SERUM LEVELS OF KETONE BODIES IN HEALTHY YOUNG MEN

Value	Level	
	mM per litre	mg. per 100 ml.
Upper limit	1·4	8·1
Typical	0·8	4·6

TABLE II—URINARY EXCRETION-RATES OF KETONE BODIES IN HEALTHY YOUNG MEN

Value	Excretion-rate			
	Per minute		Per 24 hours	
	(μM)	(μg.)	(mM)	(mg.)
Upper limit	5·0	290	7·2	418
Typical	2·5	145	3·6	209

(Tables modified from Johnson et al. 1958.)

Some ketone bodies are always present in blood and urine. Ketosis would be more accurately described as hyperketonæmia and hyperketonuria. Tables I and II give some normal values, based on studies on healthy young men. The figures may not be applicable to women.

It has been usual in the past to express results in milligrammes of acetone per 100 ml. Thinking on ketosis, as on all problems of chemical pathology, would be clearer if molar concentrations were used. The normal molar concentration of ketone bodies in serum is of the same order as that of the nonesterified fatty acids and about one-fifth that of glucose (5·5 mM per litre of glucose=100 mg. per 100 ml.) It is necessary to emphasise that values for *levels* of ketones in urine may be misleading. *Excretion-rates* reflect more accurately the blood-levels, and timed samples of urine should be collected. The nitroprusside test is very sensitive and false positives may be obtained if concentrated urines are tested. If the specimen or urine is first diluted so as to correspond to a urine flow-rate of 3 ml. per min., false positives will usually be avoided.

Factors Affecting Ketogenesis

Species Variations

Ruminants are far more liable to have ketosis than other mammals. This is almost certainly due to their relatively low level of blood-sugar. In the blood of 33 cows with ketosis, Bach and Hibbitt (1959) found the mean level of total ketones (expressed as acetone) to be 65·6 mg. per

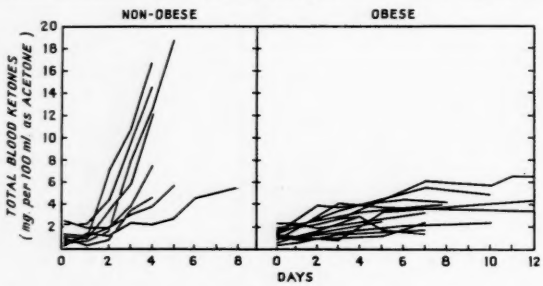

Fig. 2—Rise in blood-ketones in obese and non-obese subjects on a 1000-calorie 90%-fat diet. (Kekwick et al. 1959.)

100 ml., and the level of glucose only 28·2 mg. per 100 ml. There was an inverse relation between the severity of the disease and the blood-sugar. Increased liability to ketosis seems an inevitable result of ruminant digestion and of the associated low levels of blood-sugar. The animals are rapidly cured by the administration of glucose, and by cortisone and related substances.

Crandall (1941) found that starved dogs became ketotic much more slowly than man. Carnivores have very little carbohydrate in their natural diet and presumably can adapt more easily to carbohydrate restriction.

Obesity

Many clinicians have reported that their obese patients showed little or no ketosis when receiving reducing regimens containing very little dietary carbohydrate. Fig. 2 shows the results of a controlled study by Kekwick et al. (1959), in which the contrast between the reactions of the obese and non-obese to a ketogenic regimen is striking. This resistance to ketosis is the one and only metabolic distinction between obese patients and normal subjects which has been established beyond dispute.

Sex

Deuel and Gulick (1932) found that during fasts lasting 4 days, 5 women excreted 3 to 4 times as much urinary ketone bodies as 5 men. This appears to be the only study

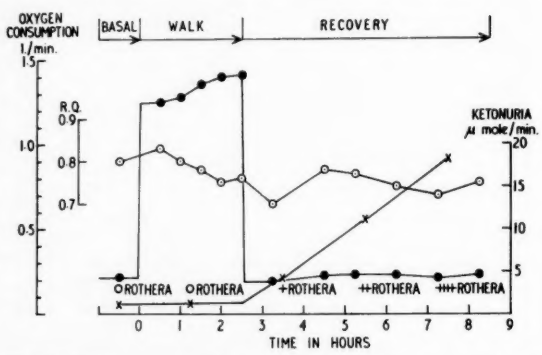

Fig. 3—Oxygen consumption, respiratory quotient, and urinary excretion of ketones, during development of postexercise ketosis.

of experimental ketosis in women. The result is surprising, especially as the women would be expected to have had a higher proportion of body fat than the men. It needs confirmation, with control of the environmental temperature and state of hydration.

Exercise

The easiest way to produce experimental ketosis in man is for the subject to arrive at the laboratory in the morning without breakfast, and then to walk for 10 miles. After resting for 1 to 2 hours after the walk, the urine in most (but not all) subjects shows a strongly positive nitroprusside reaction (fig. 3). This is known as the Courtice-Douglas effect and was first described by them in 1936 (Courtice and Douglas 1936) and has been studied more recently by Passmore and Johnson (1958). The energy expenditure during a 10-mile walk (800–1000 Calories) is roughly the same as that during a 12-hour fast. A fast as short as this seldom produces significant ketosis and probably, in addition to producing a negative calorie balance, exercise in itself is ketogenic. Johnson and Passmore (1960) report an experiment consistent with this.

Cold

That cold is a ketogenic agent was discovered by Sargent et al. (1958). They were investigating, on behalf of the American Air Force, the suitability of various " survival rations " to be used by crews after an emergency landing. Two trials were carried out, one in the winter in Wisconsin and one in the summer in Indiana: in each about 100 young men took part. After a control period of 2 weeks on a liberal diet, an experimental period of 2 weeks followed. A paired feeding technique was used, and the effects of varying the amount of daily work, the water consumption, the total calorie intake, and the percentage of calories derived from protein, fat, and carbohydrate studied

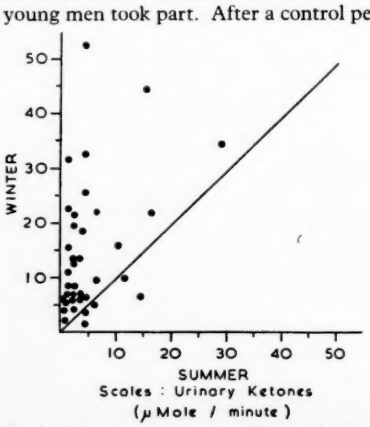

Fig. 4—Urinary excretion of total ketone bodies for three ketogenic regimens in summer and winter. (Sargent et al. 1958.)

(Sargent et al. 1958). The degree of nutritional ketosis that developed was much greater in the Wisconsin winter than in the Indiana summer (fig. 4). Cold has also been shown to be a ketogenic agent in a small laboratory investigation in Edinburgh (Passmore and Johnson 1958).

This ketogenic effect of cold may be part of a generalised response to the environment, not one specifically related to fat metabolism. It is perhaps brought about by changes in hormonal balance.

State of Hydration

In the trials of the various emergency rations, when the fluid intake was limited to 900 ml. per day, all other factors being equal, the level of ketone bodies in the serum and the urinary excretion-rates were substantially less than for well-hydrated men (fig. 5). Dehydration surprisingly appeared to be an antiketogenic agent.

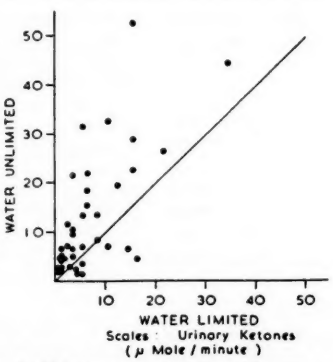

Fig. 5—Urinary excretion of total ketone bodies for three ketogenic regimens when water intake was either limited or unlimited. (Sargent et al. 1958.)

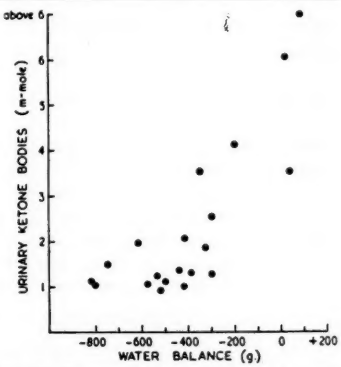

Fig. 6—Ketonuria compared with the water balance during 2½-hour walk and 6-hour recovery. (Passmore and Johnson 1958.)

This has been repeatedly confirmed in laboratory experiments on postexercise ketosis (Passmore and Johnson 1958, Johnson and Passmore 1960). As already stated, the ketogenic response to a 10-mile walk varies considerably in different persons. In these experiments, the complete water balances (fluid intake, metabolic water, urinary water, and evaporative water) were determined throughout the walk and the recovery period. In those subjects who showed little increase in urinary ketone excretion, there was always a negative water balance: this was sometimes as large as 800 ml., despite a big fluid intake. When severe ketosis developed, the subjects usually remained roughly within water balance, and sometimes even retained water (see fig. 5). The severity of ketosis was inversely related to the water balance and to the percentage of calories derived from fat during the walk (calculated from data for O_2-consumption, CO_2 production, and urinary nitrogen).

In a series of experiments on 1 subject (Johnson and Passmore 1960), the ketonuria (κ) during the recovery period, expressed in μM per min. was related by multiple correlation to the change in water balance, w, in grammes, and the percentage of calories derived from fat during the walk, c, by the equation:

$$\log \kappa = 0{\cdot}54\ w + 2{\cdot}27\ c - 0{\cdot}98$$

A correlation coefficient of 0·99 was obtained.

In the diabetic state, ketosis is closely associated with clinical dehydration, as is well known. It comes as a surprise to find that both in a field and in a laboratory study, the state of dehydration was associated with antiketogenesis. So far no satisfactory explanation of this association has been provided.

Hormones

Insulin is antiketogenic. If the supply is inadequate, as in pancreatic diabetes, ketosis develops, associated with a diminished utilisation of glucose and increased fat metabolism. The growth hormone of the anterior pituitary is ketogenic. Houssay showed in his classical experiments that hypophysectomy improved in many ways the condition of the pancreatectomised animal. It has been known for 30 years that extracts of the anterior pituitary gland were ketogenic. In the past 10 years, when pure preparations of growth hormone have become available, many observers have shown that it is ketogenic in both man and laboratory animals. In man, after injection of human growth hormones, increased urinary excretion and a raised level of blood-ketones is associated with impaired glucose tolerance, a rise in the level of the non-esterified fatty acids in the blood, and a fall in the respiratory quotient.

The effect of adrenal cortical hormones and of corticotrophin (A.C.T.H.) on ketosis is variable. In many of the reports of the action of A.C.T.H. there must be some doubt as to the interpretation of the results, because the preparation may have contained traces of growth hormone. Amatruda and Engel (1959), in a paper describing experiments on rats, conclude that the adrenal glands play, in certain circumstances, a part in promoting ketosis. The uncertainty of the action of the adrenals is illustrated by the fact that a paper from the same laboratory (Scott and Engel 1953) reports experiments on intact rats in which adrenal cortical hormones inhibited nutritional ketosis, a similar relief of bovine ketosis by cortisone is well known (Paterson 1957). In fasting ketosis in man, Kinsell et al. (1951) found that A.C.T.H. reduced the ketonæmia. Kalant (1958) found no effect of cortisone on the ketonæmia in diabetic patients, in whom both food and insulin were withheld for 24 hours. These observations show that the part of the adrenal glands in ketosis is not clear-cut.

There are other hormonal factors which may control ketosis. Stewart and Young (1959) have extracted a substance from normal muscle which induces ketonuria in normal rats on a high-fat diet. The substance appears to be a triglyceride in which a fatty-acid chain is in a partially oxidised state. Chalmers et al. (1960) have shown that there is a factor in the urine of starving human subjects which can be concentrated, and which causes ketonæmia when injected into mice. It appears to be a polypeptide, but it has chemical properties quite distinct from growth hormone.

Numerous experiments would indicate that in a great variety of circumstances many hormonal factors may modify the degree of ketosis. All that can be said with certainty is that insulin is antiketogenic, and growth hormone is ketogenic. Other hormonal factors may be in part responsible for the varying response to dietary and other environmental ketogenic agents.

Production and Utilisation of Ketone Bodies

Campbell and Best (1956) review the evidence that ketone bodies are readily oxidised in the tissues. Muscle has a large capacity for using acetoacetate as a fuel, and it is doubtful whether this capacity is ever utilised to the full. If a subject with a well-developed postexercise ketosis starts a second walk, then the muscles rapidly

oxidise the excess ketones in the body, and the blood-level soon falls to normal (Courtice and Douglas 1936, and personal observations).

Many workers have shown that ketone bodies are readily formed in the liver. This can easily be demonstrated by perfusing the isolated organ, and also by studying the metabolism of liver slices in vitro.

Thus, there is general agreement that ketosis always arises as a result of overproduction in the liver and never from a failure of utilisation by the muscles and other tissues. The causes of this overproduction in the liver present a biochemical problem, as yet unsolved.

The Biochemical Background

There are now many new ideas, which allow a fresh appraisal of the enzymic mechanisms leading to ketosis. Most of these hypotheses come from America and they are reviewed in papers by Stadie (1958), Siperstein (1958), and Tepperman and Tepperman (1958). These authors tell a consistent story, which must be correct for metabolic processes at the cellular level *under certain circumstances*. Of necessity, it is always difficult to assess how applicable a discovery based on observations of fragments of tissue and lasting for only a few hours is to the understanding of the metabolic problems of the whole animal in health and disease. At least, these new biochemical findings provide interesting hypotheses, which merit serious consideration.

The following facts are generally considered to be established:

1. Acetoacetate is not formed during the breakdown of fatty acids. It is, however, an essential stage in the synthesis of fatty acids from two-carbon fragments. The synthesis of fatty acids is not a simple enzymic reversal of the pathway by which they are broken down, but a separate and independent mechanism.

2. Fatty acids are broken down into two-carbon acetate fragments. This breakdown of the molecule does not involve intermediary substances containing four or more carbon atoms. Acetic acid itself has never been isolated from the products, but is always found conjugated with coenzyme A, as acetyl CoA.

3. Acetyl CoA molecules arise both from glucose and fatty acids. Most of the energy originally present in the glucose and fatty acid molecules is still present in the acetyl CoA molecules and can then be liberated by oxidations in the Krebs cycle. There is no evidence that acetyl CoA ever accumulates as a result of a failure of supply of any of the components of the Krebs cycle. Oxaloacetic acid, which is necessary for the entry of acetyl CoA into the cycle, was formerly supposed to be essential for antiketogenesis. Many observers have now shown that administration of oxaloacetic acid does not relieve ketosis either in laboratory animals or in human diabetes. Krebs (1960) in a full review of these aspects of ketosis concludes: " There is no evidence of underutilisation of acetyl CoA in the ketotic organism, in the sense of the reduced rate of the tricarboxylic acid cycle. The capacity of the body as a whole to burn acetate is never fully used in a resting organism."

4. Any acetyl CoA formed in excess of the immediate needs of the body for energy is utilised for the synthesis of fatty acids. The first stage in this synthesis is the formation of acetoacetyl CoA.

5. There can be three possible fates for acetoacetyl CoA. First, it can be converted back into acetyl CoA. Secondly, it can be hydrolysed to free acetoacetic acid by an enzyme " deacylase " in the liver—a reaction which is not reversible. Thirdly, it may follow the synthetic pathway and be converted into fatty acid.

6. In the conversion of acetoacetyl CoA into fatty acid, the first stage is reduction to β-hydroxybutyryl CoA. For this, the reduced form of the hydrogen-carrier diphosphopyridine nucleotide (DPNH) is necessary. Then, by the removal of one molecule of water, the unsaturated crotonyl CoA is formed. This then is further reduced to butyryl CoA, which subsequently by additions forms a long-chain fatty-acid molecule. The processes whereby acetyl CoA molecules are built up into a fatty acid molecule are illustrated in fig. 7. For the reduction of crotonyl CoA to butyryl CoA, reduced triphosphopyridine nucleotide (TPNH) is needed.

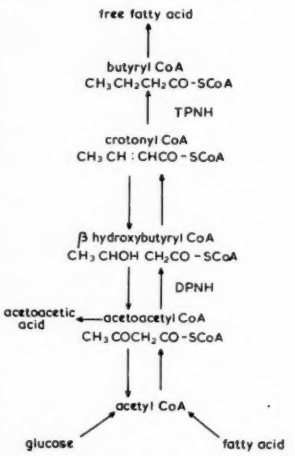

Fig. 7—Pathway for the build-up of fatty acids.

The key paper on fatty acid biosynthesis is that of Langdon (1957); he used rat-liver cells and showed that, whereas the oxidative pathway exists in the mitochondria, the synthesis takes place in soluble cytoplasm, and may take place exclusively here. In this process TPNH serves as an electron donor for the reduction of the unsaturated crotonyl CoA to the saturated butyryl derivative.

Abnormal metabolic states, which are accompanied by decreased rates of TPN reduction, may also be accompanied by decreased rates of fatty acid synthesis. This may be extended to the hypothesis that ketosis arises whenever there is insufficient TPNH to effect fat synthesis. A block will then arise, and cause acetoacetyl CoA to accumulate, and from this the enzyme deacylase in the liver produces free acetoacetic acid. In this scheme TPNH appears as a key antiketogenic substance.

TPNH and the Pentose-phosphate Shunt

Students have long been taught that glucose is converted into pyruvic acid, the immediate precursor of acetyl CoA, by the Embden-Meyerhof pathway. In this route, the intermediary stages include glucose 6-phosphate, fructose 6-phosphate, and glyceraldehyde phosphate. More recently an alternative pathway known as the pentose-phosphate shunt has been discovered. In this, glucose 6-phosphate is first converted into pentose phosphate, from which, after a complex series of intermediary reactions, pyruvate is formed. For the formation of pyruvate by any route, hydrogen has to be removed from the glucose molecule. In the Embden-Meyerhof pathway, oxidised DPN serves as the effective agent. In the pentose-phosphate shunt, the oxidised form of TPN is used with the resulting production of TPNH. Glycolysis, via the pentose-phosphate shunt, thus provides the tissues with a supply of TPNH, which can then function as an antiketogenic agent. Dickens et al. (1959) give a full account of the alternative pathways of carbohydrate metabolism.

The Embden-Meyerhof pathway and the pentose-phosphate shunt provide another of the many examples of how the body has apparently alternative mechanisms for carrying out a single function. As yet, there is little knowledge of the proportions of glucose which use each pathway in the intact animal under varying circumstances, though it is generally assumed that the simpler Embden-Meyerhof pathway is the more used.

Isotopic studies can be of some help. In the pentose-phosphate shunt, the C_1 carbon atom in the glucose molecule is first removed and appears as CO_2. In the Embden-Meyerhof

pathway, it is the C_6 carbon atom in the glucose molecule that gives rise to CO_2. If $^{14}C_1$ and $^{14}C_6$ glucose are given to a system, the relative amounts of $^{14}CO_2$ that are produced give a measure of the relative amounts of glucose going down each route.

Discussion

These new observations on the behaviour of enzymic systems at the cell level would appear to have defined the problem of ketosis more sharply, but not to have provided any solution. There are certainly sources of TPNH available to the body other than from the pentose-phosphate shunt: there are also demands for it as a reducing agent for other processes besides fatty acid synthesis. In some circumstances (Siperstein 1957) TPNH takes part in cholesterol synthesis. This is an observation which promotes speculation on the manifold problems of the chemical pathology of diabetes, a disease in which a high level of plasma-cholesterol is so often found.

The problem still remains of the relative value of fat and carbohydrate as a source of fuel for the body. In the diet of modern industrial societies, carbohydrate provides about 50% of the calories, and fat just under 40%. Individuals can live in health on diets widely different from these mean figures. Both fatty acid and glucose can certainly act as a fuel for the tissues with about the same degree of efficiency, which in general compares well with the efficiency of fuels used by other "engines". The most obvious difference between the physiology of fat and that of carbohydrate is the ability of the body to store large quantities of one and very little of the other. In man, the stores of fat are 20 to 50 times greater than those of carbohydrate. Triglycerides and polysaccharides are being continuously broken down from these stores to provide fatty acids and glucose, which are taken to the tissues for fuel. Surpluses of these substances are resynthesised into storage material, but with the difference that synthesis of fat is normally relatively easily accomplished in large quantities, whereas carbohydrate synthesis is always strictly limited. We do not know at all accurately the rates of turnover of the stores in the intact body under physiological conditions: they are probably rapid and may well exceed that necessary for satisfying the immediate needs of the tissues for fuel. The mechanisms regulating the supply of fuel from the stores to the tissue normally may operate, not on the processes of mobilisation but rather on those of deposition. In the cell, synthesis may take place in the cytoplasm, whereas oxidative breakdown appears to be effected in the mitochondrial particles. Hormones—e.g., insulin, adrenaline, growth hormone, adrenocortical hormone—certainly regulate mobilisation and deposition of carbohydrate and fat. Yet it is still impossible to describe with any confidence the chemical manner in which these hormones effect the movements of material in and out of the stores.

An explanation in biochemical terms of the physiological factors which lead to ketosis must await the future. There is still the paradox that though clinically (especially in diabetes) ketosis is associated with dehydration, yet in experiments with healthy young men dehydration has been shown to be an antiketogenic factor. The obese patients' relative resistance to nutritional ketosis may be due to a large supply of TPNH from active use of the pentose-phosphate pathway, or they may have other sources of this essential factor. A disproportion in the amounts of carbohydrate normally metabolised via the Embden-Meyerhof pathway and via the shunt might contribute to the onset of obesity.

The appearance of ketosis remains a valuable clinical signal of a disturbed metabolism. Yet the nature of the possible disturbances still await clear definition. There are observations which suggest that the pentose-phosphate shunt may be of great importance to an understanding of some clinical phenomena. Prophecy is always dangerous, but I will risk ending with the guess that the shunt will soon become "news" far beyond biochemical laboratories. It may not be long before some sophisticated valetudinarian begins a consultation with his general practitioner thus: "Say, Doc, I want a check-up on my pentose shunt."

Summary

The onset of ketosis is now known to depend on a number of factors, and not simply on the ratio of fat to carbohydrate in the diet.

The primary ketone body is acetoacetic acid, which is enzymatically reduced to β-hydroxybutytate in the tissues. Both substances are present in the urine during ketosis, the amount of β-hydroxybutyrate increasing with the severity of the ketosis.

The factors involved in the production of ketosis include: species variation, obesity, sex, exercise, thermal changes, degree of hydration, and the effect of some hormones—e.g., insulin and corticotrophin. Their complex interactions and relations are difficult to assess experimentally, and the results obtained are often conflicting.

It is suggested that ketosis arises whenever there is insufficient reduced triphosphopyridine nucleotide (TPNH) to effect fat synthesis. An important source of TPNH is the pentose-phosphate shunt—an alternative route to the Embden-Meyerhof pathway by which glucose is converted to pyruvic acid. The body can apparently make use of either pathway to varying extents which depend on circumstances not yet elucidated.

The pentose-phosphate shunt seems of great importance in the understanding of some clinical phenomena, but an explanation in biochemical terms of the physiological factors which lead to ketosis has yet to be produced.

REFERENCES

Amatruda, T. T., Engel, F. L. (1959) *Yale J. Biol. Med.* **31**, 303.
Bach, S. J., Hibbitt, K. G. (1959) *Biochem. J.* **72**, 87.
Campbell, J., Best, C. H. (1956) *Metabolism*, **5**, 95.
Chalmers, T. M., Pawan, G. L. S., Kekwick, A. (1960) *Lancet*, ii, 6.
Courtice, F. C., Douglas, C. G. (1936) *Proc. roy. Soc. B.* **119**, 381.
Crandall, L. A. (1941) *J. biol. Chem.* **138**, 123.
Deuel, J. R., Gulick, M. (1932) *ibid.* **96**, 25.
Dickens, F., Glock, G. E., McLean, P. (1959) *in* Symposium on the Regulation of Cell Metabolism. Edited by G. E. W. Wolstenholme and C. M. O'Connor. London.
Johnson, R. E., Sargent, F., Passmore, R. (1958) *Quart. J. exp. Physiol.* **43**, 339.
— Passmore, R. (1960) *Metabolism*, **9**, 443.
Kalant, N. (1958) *Lancet*, ii, 925.
Kekwick, A., Pawan, G. L. S., Chalmers, T. M. (1959) *ibid.* ii, 1157.
Kinsell, L. W., Margen, S., Michaels, G. D., Reiss, R., Frank, R., Carbone, J. (1951) *J. clin. Invest.* **30**, 1491.
Krebs, H. A. (1960) *Proc. R. Soc. Med.* **53**, 71.
Langdon, R. G. (1957) *J. biol. Chem.* **226**, 615.
Passmore, R., Johnson, R. E. (1958) *Quart. J. exp. Physiol.* **43**, 352.
Paterson, R. A. (1957) *Vet. Rec.* **69**, 1097.
Rothera, A. C. H. (1908) *J. Physiol.* **37**, 491.
Sargent, F., Johnson, R. E., Robbins, E., Sawyer, L. (1958) *Quart. J. exp. Physiol.* **43**, 345.
Scott, J. L., Engel, F. L. (1953) *Endocrinology*, **53**, 410.
Shaffer, P. A. (1921) *J. biol. Chem.* **49**, 143.
Siperstein, M. D. (1958) *Diabetes*, **7**, 181.
— (1957) *Amer. J. Med.* **22**, 974.
Stadie, W. C. (1958) *Diabetes*, **7**, 173.
Stewart, H. B., Young, F. G. (1959) *Biochem. J.* **72**, 60.
Tepperman, H. M., Tepperman, J. (1958) *Diabetes*, **7**, 478.
Thin, C., Robertson, A. (1952) *Biochem. J.* **51**, 218.

ACTION OF HEPARIN IN ISCHÆMIC HEART-DISEASE

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THIS investigation was made to compare the initial effect of heparin given intravenously on blood coagulation in patients with ischæmic heart-disease and in normal people, and to determine any anticoagulant effect of small doses of heparin given over a long period in such patients (McDonald 1960). Coagulability of the blood, with particular regard to thromboplastin generation, platelet stickiness, and fibrinogen estimation, is increased in patients with ischæmic heart-disease compared with healthy people (McDonald 1957, McDonald and Edgill 1957), particularly after recent cardiac infarction (McDonald and Edgill 1959). Possible explanations for these findings were that patients with ischæmic heart-disease might be deficient in heparin through using too much or not producing enough, or that they might metabolise heparin in a different way from normal people.

Material

Under standard conditions the effect of an intravenous dose of heparin was compared in men with ischæmic heart-disease and healthy men of similar age; thereafter the results of small intramuscular doses of heparin, given to the patients for 6 months, were studied.

The patients and normal men, who acted as controls, were ambulant and attended as outpatients for samples of blood to be taken at 9.30 A.M. They were instructed to have only a light breakfast—i.e., tea or coffee and toast, with no cream and very little butter—on the morning of their test. Blood was withdrawn from an antecubital vein into an oiled syringe; samples were accepted only if there had been a clean venepuncture and an uninterrupted flow of blood into the syringe.

Effect of Initial Injection of Heparin

Seven healthy men and eight male patients with ischæmic heart-disease were compared. Six of the patients had had past cardiac infarction, and none had had recent infarction. The healthy men and the patients were aged 45–60 years (average 54·0). The healthy men weighed 142–195 lb. (average 175), and the patients 130–175 lb. (average 154). After an initial dose of 10,000 units of heparin intravenously blood was taken at intervals of 30 and 60 minutes for estimation of thromboplastin generation.

Effect of Small Doses of Heparin for a Long Term

Six of the above patients with ischæmic heart-disease (cases 1, 3, 4, and 6–8), and two others, neither of whom had had past cardiac infarction, were studied for 6 months. An initial intravenous injection of 10,000 units of heparin was followed after 4 hours by the subcutaneous injection of 5000 units of heparin, and thereafter by 1000–1500 units intramuscularly twice weekly.

Initially the thromboplastin-generation test with intravenous heparin was performed, and the platelet-count and stickiness, modified whole-blood clotting-time, and serum-cholesterol were estimated. These tests were repeated at intervals of 1–4 weeks, and titration with protamine sulphate, for heparin, was performed on some occasions. Once patients were having heparin intramuscularly, blood was always taken for further coagulation tests at least 60 hours after the last injection of heparin.

Methods

All tests of blood coagulation were performed as described by McDonald and Edgill (1957), with later modifications (McDonald and Edgill 1958). Platelet stickiness was estimated at 20 minutes only. Platelet suspensions (Biggs and Macfarlane 1957) were prepared from the blood of each patient and control, and substituted for the chloroform extract of brain in the thromboplastin-generation test. The effect of intravenous heparin on thromboplastin generation was determined in each patient and control using a method similar to that of Ulutin and Sestakof (1957):

30 ml. of venous blood was taken into an oiled syringe for an initial thromboplastin-generation test, and to provide substrate plasma for subsequent thromboplastin-generation tests. The syringe containing the blood was removed leaving the needle in the vein, heparin 10,000 international units was injected, and the time was noted. Further samples of blood were taken 30 and 60 minutes after the injection of heparin for estimation of thromboplastin generation. Blood taken before the injection of heparin was always used to provide the substrate plasma for all three estimations of thromboplastin generation, and the use of a platelet suspension was essential.

A modification of Lee and White's (1913) method (Warren and Wysocki 1958) was used to estimate the whole-blood clotting-time:

1 ml. of whole blood was placed in each of three glass tubes (diameter $^3/_8$ in.) containing a small glass bead. The first test-tube

TABLE I—THROMBOPLASTIN GENERATION IN MEN WITH ISCHÆMIC HEART-DISEASE AND IN HEALTHY MEN BEFORE AND AFTER HEPARIN 10,000 UNITS INTRAVENOUSLY
(Findings are expressed as % of thromboplastin: 7·8 sec. = 100%)

Incubation time (min.)	Before I.V. heparin												30 min. after I.V. heparin												60 min. after I.V. heparin											
	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12
Patient 1	3	55	120	120	120	120	120	116	113	108	104	104	1	1	2	3	7	34	40	40	40	34	34	34	1	1	2	3	30	58	80	80	80	76	58	58
Control 1	1	3	12	100	100	97	96	93	87	80	76	70	1	1	1	2	3	3	4	11	11	11	11	11	1	1	2	3	3	4	11	11	11	11	11	11
Patient 2	1	2	5	113	108	106	106	106	106	106	106	106	1	2	7	37	41	45	45	45	45	45	45	45	2	10	95	104	104	104	104	104	104	104	104	100
Control 2	2	4	100	100	100	100	97	97	97	97	95	95	2	2	10	43	43	57	57	57	57	57	57	57	2	4	30	45	56	56	56	56	56	56	56	48
Patient 3	2	3	24	112	112	105	100	100	100	100	98	95	2	3	47	60	57	57	57	55	50	46	44	42	2	4	55	90	85	80	75	64	55	46	42	38
Control 3	2	3	20	95	95	95	90	90	90	85	85	85	1	2	4	20	29	29	29	29	29	27	27	25	2	4	22	30	30	30	30	30	30	27	25	23
Patient 4	2	4	20	100	110	115	104	100	98	98	98	98	4	30	42	48	60	60	60	60	60	60	60	60	2	25	100	100	110	110	100	100	98	98	95	95
Control 4	3	15	100	104	100	100	100	100	100	100	100	100	3	11	37	42	58	58	58	58	58	50	50	50	1	2	10	55	70	70	70	70	65	65	60	50
Patient 5	3	52	120	120	120	120	120	120	112	105	105	102	3	4	9	52	52	52	52	52	52	52	52	52	2	3	4	82	82	78	65	65	65	65	52	48
Control 5	3	9	98	95	95	95	90	90	90	87	87	87	1	2	5	12	20	22	22	22	22	22	20	16	1	1	2	3	9	13	13	13	13	13	13	13
Patient 6	2	5	113	115	115	115	113	113	106	106	106	100	2	2	5	37	42	48	50	50	50	50	45	43	1	2	5	80	80	80	80	80	76	76	76	76
Control 6	2	7	100	99	97	97	95	90	90	90	90	90	1	2	2	3	20	38	45	45	45	45	45	40	1	2	3	3	20	38	54	54	54	50	45	42
Patient 7	2	17	118	115	115	115	115	110	110	110	105	105	1	1	2	4	20	29	30	30	30	30	30	27	2	4	95	98	98	95	95	95	90	90	85	75
Control 7	2	3	9	48	80	80	80	60	45	45	45	45	1	2	3	4	4	4	4	4	4	4	4	3	1	2	3	3	4	4	4	4	4	4	4	3
Patient 8	1	2	5	95	106	115	115	115	115	115	106	100	1	1	2	8	42	49	49	49	49	49	45	40	1	1	2	14	63	75	85	85	85	85	85	80
Control 8	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..

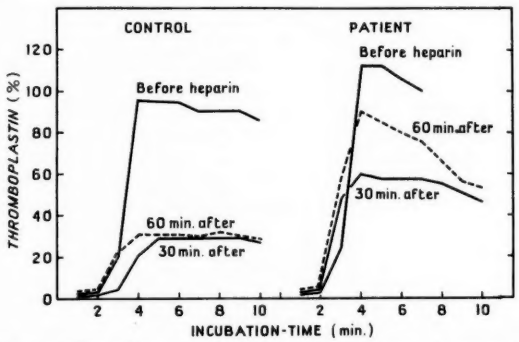

Fig. 1—Effect of intravenous heparin on thromboplastin generation in a patient with ischæmic heart-disease, and in a normal control (see text).

was gently tilted every 30 sec. until the blood in it had clotted. The second tube, which had been standing at 37°C, was then similarly treated until the blood in it had clotted. The third tube, which itself had been standing until this time, was then tilted, and the clotting-time of this blood was recorded.

Heparin was estimated by protamine titration (Dr. A. A. Sharp, personal communication 1959):

A solution of protamine sulphate in distilled water, containing 20 mg. per 100 ml., was freshly prepared for each estimation. Dilutions of this solution were made in physiological saline, to contain 20, 10, 5, 4, 3, 2, 1, and 0·5 μg. of protamine sulphate per 0·1 ml. solution. A human thrombin ('Fibrindex') solution in saline was prepared containing 10 units per ml. The level of heparin was estimated in citrated plasma; the plasma was prepared as described earlier (McDonald and Edgill 1957). A series of clotting mixtures were placed in a water bath at 37°C; these contained 0·2 ml. test plasma (citrated 1/10), 0·1 ml. protamine sulphate dilution (20–0·5 μg.), and 0·1 ml. physiological saline. 0·1 ml. of the thrombin solution was added to each, and the clotting-times were recorded. A sudden change in the recorded clotting-times indicates the "break" point. At this dilution the protamine sulphate neutralises the heparin, and thus the amount of heparin present can be estimated. One part of heparin is assumed to be neutralised by one part of protamine sulphate, thus:

$$\frac{\text{Protamine sulphate } \mu\text{g.}}{2} = \text{Heparin (mg. per 100 ml. of plasma)}$$

Serum-cholesterol was estimated by Abell's method (Abell et al. 1952), which was modified by letting the tubes stand at room temperature for 20–30 minutes, instead of slowly centrifuging, to separate the ethereal and aqueous layers.

Results

Effects of Initial Injection of Heparin

The results of the thromboplastin-generation test before, and 30 and 60 minutes after, the intravenous injection of heparin 10,000 units are shown in table I. Heparin depresses thromboplastin-generation to a lesser extent, and for a shorter time in patients with ischæmic heart-disease than in normal men (fig. 1 and table I). In the patients the peak achieved in the thromboplastin-generation test was never less than 80% at 60 minutes. In the normals it never exceeded 70%. Thus, with regard to thromboplastin generation at 60 minutes after 10,000 units of heparin intravenously, the two groups behaved differently. When each patient was compared with his control, the difference in the peak percentage achieved in the thromboplastin-generation test at 60 minutes, was from 94 to 26%. The values for patients and controls never overlapped.

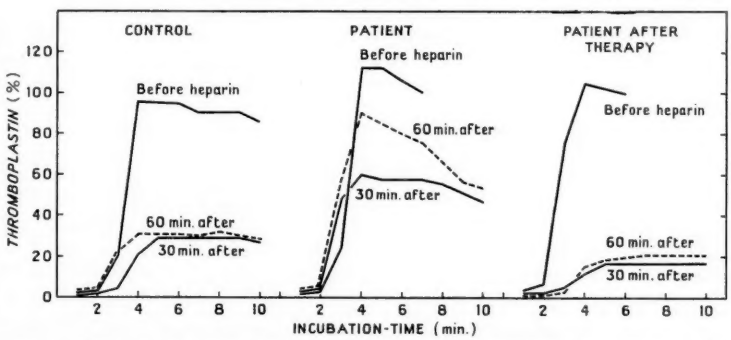

Fig. 2—Effect of intravenous heparin on thromboplastin generation in a patient with ischæmic heart-disease after long-term heparin therapy, compared with the findings in the same patient before therapy and in a normal control (see text).

TABLE II—THROMBOPLASTIN GENERATION BEFORE AND AFTER HEPARIN 10,000 UNITS INTRAVENOUSLY IN HEALTHY MEN AND IN PATIENTS WITH ISCHÆMIC HEART-DISEASE, BEFORE AND AFTER LONG-TERM HEPARIN

(Findings are expressed as % of thromboplastin: 7·8 sec. = 100%)

Incubation time (min.)		Before I.V. heparin												30 min. after I.V. heparin												60 min. after I.V. heparin											
		1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12
Control		1	3	12	100	100	97	96	93	87	80	76	70	1	1	1	2	3	3	4	11	11	11	11	11	1	1	2	3	3	4	11	11	11	11	11	11
Patient 1:	A	3	55	120	120	120	120	120	116	113	108	104	104	1	1	2	3	7	34	40	40	40	34	34	34	1	1	2	3	30	58	80	80	80	76	58	58
	B	2	2	20	112	112	112	112	112	112	112	112	112	2	3	30	37	50	50	50	50	50	50	50	50	2	4	50	65	75	80	80	80	80	80	75	65	60
	C	2	30	90	90	90	90	90	82	82	82	82	82	1	7	33	33	33	33	33	33	33	33	33	33	1	2	8	33	33	33	33	33	33	30	30	30
Control		2	3	20	95	95	95	90	90	90	85	85	85	1	2	4	20	29	29	29	29	29	27	27	25	2	4	22	30	30	30	30	30	30	27	25	23
Patient 3:	A	2	3	24	112	112	105	100	100	100	100	98	95	2	3	47	60	57	57	57	55	50	46	44	42	2	4	55	90	85	80	75	64	55	46	42	38
	B	2	3	17	110	104	100	95	90	88	88	82	78	1	2	3	22	24	27	27	27	27	27	27	24	1	2	4	20	24	28	28	28	27	27	27	23
	C	3	6	75	105	100	100	100	100	100	100	100	100	2	2	4	12	17	17	17	17	17	17	17	17	1	2	3	14	17	18	20	20	20	20	20	20
Control		3	15	100	104	100	100	100	100	100	100	100	100	3	11	37	42	58	58	58	58	58	50	50	50	1	2	10	55	70	70	70	70	65	65	60	50
Patient 4:	A	2	4	20	100	110	115	104	100	98	98	98	98	4	30	42	48	60	60	60	60	60	60	60	60	2	25	100	100	110	110	100	100	98	98	95	95
	B	1	3	20	33	35	35	33	31	30	25	22	20	1	1	1	2	4	5	6	6	6	6	6	6	1	1	5	25	35	35	30	27	25	25	25	25
	C	3	16	120	120	120	120	118	118	118	115	110	100	1	1	3	14	25	25	25	25	25	24	22	19	1	3	25	33	32	32	32	32	30	24	22	20
Control		2	7	100	99	97	97	95	90	90	90	90	90	1	2	2	3	20	38	45	45	45	45	45	40	1	2	3	3	20	38	54	54	54	50	45	42
Patient 6:	A	2	5	113	115	115	115	113	113	106	106	106	100	2	2	5	37	42	48	50	50	50	50	45	43	1	2	5	80	80	80	80	80	76	76	76	76
	B	2	5	100	100	100	100	100	100	100	100	100	98	1	1	1	2	3	10	20	20	20	20	20	20	1	1	2	5	13	21	21	21	20	17	17	17
	C	2	20	104	104	108	108	104	104	104	100	100	100	1	1	3	12	25	25	25	25	25	25	25	25	1	4	25	37	45	45	45	45	45	45	45	45
Control		2	3	9	48	80	80	80	60	45	45	45	45	1	2	3	4	4	4	4	4	4	4	4	3	1	2	3	3	4	4	4	4	4	4	4	3
Patient 7:	A	2	17	118	115	115	115	115	110	110	110	105	105	1	1	2	4	20	29	30	30	30	30	30	27	2	4	95	98	98	95	95	95	90	90	85	75
	B	3	8	85	98	92	92	85	65	53	48	48	48	2	2	3	4	7	13	20	20	20	19	15	13	2	3	4	34	43	58	58	58	58	58	48	48
	C	3	8	55	68	68	68	68	62	55	50	47	40	2	2	3	5	13	19	22	22	22	22	19	17	1	3	4	22	29	29	29	29	29	29	29	29
Control		..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Patient 8:	A	1	2	5	95	106	115	115	115	115	115	106	100	1	1	2	8	42	49	49	49	49	49	45	40	1	1	2	14	63	75	85	85	85	85	85	80
	B	2	30	100	100	100	100	100	100	100	100	100	95	1	2	3	17	38	38	38	38	38	38	38	35	2	4	25	33	34	34	34	34	34	34	34	32
	C	1	3	4	42	100	98	95	95	95	95	95	95	1	1	2	4	15	20	23	23	23	23	23	23	1	1	2	3	9	21	23	23	23	23	23	23

A = Before long-term heparin; B = after 3 months' long-term heparin; C = after 6 months' long-term heparin.

TABLE III—PLATELET STICKINESS IN MEN WITH ISCHÆMIC HEART-DISEASE BEFORE AND AFTER LONG-TERM HEPARIN THERAPY

Patient no.	% of initial platelet-count remaining at 20 min.		
	Before heparin	After 3 months' heparin	After 6 months' heparin
1	62	81	82
3	68	79	79
4	64	80	79
6	64	77	89
7	60	83	83
8	61	83	68
9	61	80	80
10	55	76	72

Effects of Small Doses of Heparin for a Long Term

In all patients the effect of intravenous injection of heparin on thromboplastin generation returned to normal, or nearly normal, after long-term heparin. The findings in a typical patient are given in fig. 2, and the results for the remainder in table II. Platelet stickiness, which had previously been increased, returned to the normal range in all patients after long-term heparin (table III). No significant change was found in platelet-counts or in serum-cholesterol. There was a slight and significant lengthening of the whole-blood clotting-time (table IV).

The results of protamine titration for heparin in three patients are shown in table V; in only one was any heparin found in the blood before the intravenous dose. After the intravenous dose larger amounts were always found, as might be expected. In six observations heparin was not detected by this method in normal people.

Thus after intravenous heparin thromboplastin generation remained much more active in patients with ischæmic heart-disease than in healthy people. This response returned to normal after remarkably small doses of heparin for a long term. The values for platelet stickiness also became normal in these patients, both changes occurring without a clinically significant lengthening of the whole-blood clotting-time.

TABLE IV—WHOLE-BLOOD CLOTTING-TIMES IN MEN WITH ISCHÆMIC HEART-DISEASE BEFORE AND AFTER LONG-TERM HEPARIN THERAPY

Patient no.	Whole-blood clotting-times (min.) (normal 9–17 min.)		
	Before heparin	After 3 months' heparin	After 6 months' heparin
1	8·0	11·0	19·0
3	15·5	14·0	15·0
4	12·0	18·0	13·5
6	12·0	13·0	19·0
7	13·5	17·0	15·0
8	10·0	16·0	17·5
9	—	15·5	15·5
10	9·5	17·5	17·5

Discussion

Enhanced coagulability of the blood in patients with ischæmic heart-disease has been shown to be reduced by small doses of heparin over a long term, without clinically significant prolongation of the whole-blood clotting-time beyond the normal range.

We must emphasise that our study provides no evidence that such heparin therapy will affect the morbidity or mortality of ischæmic heart-disease. It may do so, but any such hypothesis will demand a more extensive clinical trial. Such anticoagulant treatment, if effective, could prove safe and need little laboratory control. One patient (no. 5) having long-term heparin therapy, who had had previous cardiac infarction, died suddenly after 5 months, but a postmortem was not obtained. Death was presumed to be due either to further cardiac infarction or to ventricular fibrillation. There was no evidence to suggest hæmorrhage. In another patient (no. 2) the dose of heparin was temporarily augmented during a period of chronic coronary insufficiency, from which he recovered. We have observed that more heparin is needed to maintain thromboplastin generation and platelet stickiness at normal levels during acute phases of ischæmic heart-disease and during active intravascular thrombosis. In none of the patients reported can the altered response to intravenous heparin be attributed to a lesser demand for heparin after recovery from recent cardiac infarction.

TABLE V—PLASMA-HEPARIN LEVELS IN PATIENTS WITH ISCHÆMIC HEART-DISEASE BEFORE AND AFTER LONG-TERM HEPARIN THERAPY

Patient no.	Plasma-heparin (mg. per 100 ml.)					
	After 3 months' heparin			After 6 months' heparin		
	Before I.V. heparin	30 min. after I.V. heparin	60 min. after I.V. heparin	Before I.V. heparin	30 min. after I.V. heparin	60 min. after I.V. heparin
3	—	—	—	0	1·50	1·00
4	0·25	1·25	0·50	0	2·00	1·50
7	0·00	2·00	1·50	0	2·00	1·50

The action of heparin on blood coagulation and thrombosis, and its fate in the body, have not yet been adequately investigated. Heparin may release the anticoagulant phosphatide-inhibitory fraction (Overman 1949), interfere with prothrombin conversion (Douglas 1956), depress thromboplastin generation (Shanberge et al. 1959), or act on Christmas factor (O'Brien 1958). The blood may show increased coagulability after thrombosis and embolism (Poller 1956, McDonald and Edgill 1957), and this may be connected with an alteration in the antiheparin action of platelets that is well documented (van Creveld and Paulssen 1951, Stefanini 1953, Deutsch 1954, van Creveld 1954, Vandenriessche 1959). Heparin may be required to neutralise the antiheparin platelet factor or to react with an excess of Christmas factor in these patients, and the heparin given in our study may have fulfilled such biological needs. Certainly heparin diminishes the incidence of venous thrombi (Murray et al. 1937). We have found (unpublished) that increased thromboplastin generation in ischæmic heart-disease is due to a serum factor or factors, and Poller (1957) has suggested that resistance to heparin after recent thrombosis was on the basis of increased factor VII activity. Earlier observations by Wessler (1955) supported Poller's (1957) thesis, but recently Wessler and Reimer (1960) have suggested that a serum-thrombotic-accelerator factor is responsible. It is surprising that the small infrequent doses of heparin used in our long-term investigation produced the changes demonstrated; it might be assumed that heparin given in this way would be quickly excreted by the kidneys or detoxicated by the liver (Eiber and Danishefsky 1958). Although we did not always demonstrate circulating heparin in patients on long-term therapy, we have never done so in normals, although heparin has been claimed as a normal constituent of blood (Jaques et al. 1953).

Ulutin and Sestakof (1957) described a difference between patients with ischæmic heart-disease and normals with regard to thromboplastin generation after intravenous heparin. Our findings completely support their work and we have shown that the abnormality is reversible. The modification of the thromboplastin-generation test used appears much more reliable than the heparin-tolerance test, which has yielded comparable results in ischæmic heart-disease (Beaumont et al. 1953).

The decrease in platelet stickiness could be due to the adsorption of heparin on to the platelets' surface. From our earlier observations it seems likely that any measure which will revert platelet stickiness to normal might lessen the likelihood of intravascular thrombi.

We consider that the effects demonstrated represent a radical change in blood coagulation in these patients, indicating a different response to heparin in patients with ischæmic heart-disease as compared with healthy men of the same age.

Summary

The action of intravenous heparin on thromboplastin generation has been compared in men with ischæmic heart-disease and normal men. The effect of small intramuscular doses of heparin over a long term has been investigated in patients with ischæmic heart-disease, in relation to thromboplastin generation, before and after intravenous injection of heparin, platelet-count and stickiness, modified whole-blood clotting-time, and serum-cholesterol.

The initial intravenous dose of heparin depressed thromboplastin generation to a lesser extent, and for a shorter time, in patients with ischæmic heart-disease than in normal men. After long-term heparin therapy this response in patients returned to normal, and platelet stickiness (previously abnormal) also returned to normal, both without clinically significant lengthening of the whole-blood clotting-time. The levels of serum-cholesterol did not alter. The changes demonstrated after long-term heparin represent a radical alteration in blood coagulation in patients with ischæmic heart-disease, and they are discussed with regard to the action of heparin on blood coagulation and thrombosis.

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REFERENCES

Abell, L. L., Levy, B. B., Brodie, B. B., Kendall, F. E. (1952) *J. biol. Chem.* **195,** 357.
Beaumont, J. L., Chevalier, H., Lenègre, J. (1953) *Amer. Heart J.* **45,** 756.
Biggs, R., Macfarlane, R. G. (1957) Human Blood Coagulation and its Disorders; p. 394. Oxford.
Deutsch, E. (1954) *Rev. hémat.* **9,** 483.
Douglas, A. S. (1956) *J. clin. Invest.* **35,** 533.
Eiber, H. B., Danishefsky, I. (1958) *Arch. intern. Med.* **102,** 189.
Jaques, L. B., Napke, E., Levy, S. W. (1953) *Circ. Res.* **1,** 321.
Lee, R. I., White, P. D. (1913) *Amer. J. med. Sci,* **145,** 495.
McDonald, L. (1957) *Brit. Heart J.* **19,** 584.
— (1960) Proceedings of the Third European Congress of Cardiology, Rome; Pars Altera A. p. 113.
— Edgill, M. (1957) *Lancet,* ii, 457.
— — (1958) *ibid.* i, 996.
— — (1959 *ibid.* i, 1115.
Murray, D. W. G., Jaques, L. B., Perrett, T. S., Best, C. H. (1937) *Surgery,* **2,** 163.
O'Brien, J. R. (1958) *Nature, Lond.* **181,** 1801.
Overman, R. S. (1949) Blood Clotting and Allied Problems; 2nd Conference, Josiah Macy, Jr., Foundation; p. 29.
Poller, L. (1956) *Clin. Sci.* **15,** 55.
— (1957) *J. clin. Path.* **10,** 348.
Shanberge, J. N., Sarelis, A., Regan, E. E. (1959) *J. Lab. clin. Med.* **54,** 501.
Stefanini, M. (1953) *Amer. J. Med.* 14, 64.
Ulutin, O. N., Sestakof, D. (1957) *Bull. Soc. turq. Méd.* **23,** 689.
van Creveld, S. (1954) *Acta hæmat.* **12,** 229.
— Paulssen, M. M. P. (1951) *Lancet,* ii, 242.
Vandenriessche, R. (1959) *Acta med. scand.* **165,** 217.
Warren, R., Wysocki, A. (1958) *Surgery,* **44,** 435.
Wessler, S. (1955) *J. clin. Invest.* **34,** 647.
— Reimer, S. M. (1960) *ibid.* **39,** 262.

A NEW SYNTHETIC PENICILLIN PA-248

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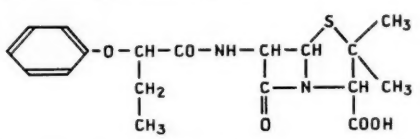
a-PHENOXYPROPYL penicillin (PA–248) is a new synthetic penicillin. Its potential therapeutic value has been assessed by determination of its antibacterial spectrum in vitro, in conjunction with measurements of serum levels after oral administration.

In recent years two distinct methods of assessing the merits of antibiotics have been advocated. Garrod (1960a) recommends the determination of the weight of antibiotic per unit volume of serum, together with measurements of its in-vitro antibacterial activity against a wide variety of organisms. Kunin, Dornbush and Finland (1959), however, suggest that the antibacterial activity per unit volume of serum should be measured in serum samples derived from subjects who have received the drug. This activity measurement is referred to that of a standard antibiotic, in this case penicillin G.

The investigations reported here have been undertaken in accordance with both methods, and, in consequence, the results are expressed both in terms of weight and of international units of penicillin-G activity. Furthermore, in all experiments, a comparison has been made with the two oral penicillins in current use—namely, penicillin V and phenethicillin.

The structural formula of PA–248 is:—



The molecular weight of this compound is 378·4, and it occurs as a mixture of two optically active isomers. The potassium salt, used in these experiments, is readily soluble in water and extremely stable in the presence of acid.

Methods

Blood-level Studies

Two distinct blood-level studies, each of triple-crossover design, were undertaken, using single 250 mg. doses (as the potassium salt) of penicillin V, phenethicillin, and PA–248.

The three phases of each crossover study were separated by an interval of 7 days. During these 7-day intervals and in the 7 days preceding the study, no subject received any chemotherapeutic agent. Thus, at the completion of the study, all subjects had received single doses of all three penicillins.

In the first study (16 subjects), blood-samples were withdrawn 1, 2, 4, and 6 hours after administration of the penicillin, and the antibacterial activity of each sample was measured in terms of international units of penicillin G.

In the second study (12 subjects), the weight of antibiotic per unit volume of serum was determined in addition to the antibacterial activity. In this study, however, no 6-hour samples were taken, because the earlier study demonstrated that none of the penicillins gave a detectable serum level 6 hours after the administration of a single 250 mg. dose.

TABLE I—SERUM CONCENTRATIONS (GARROD METHOD) (μg. per ml.) OF PA–248, PHENETHICILLIN, AND PENICILLIN V FOLLOWING ORAL ADMINISTRATION OF A SINGLE 250 mg. DOSE

Subject no.	Hours after administration								
	1			2			4		
	Penicillin V	Phenethicillin	PA–248	Penicillin V	Phenethicillin	PA–248	Penicillin V	Phenethicillin	PA–248
1	2·80	9·90	11·40	0·33	2·80	4·00	N.D.	0·41	0·80
2	1·52	8·50	11·40	0·82	1·50	3·60	0·70	0·70	0·70
3	1·85	2·60	9·00	0·14	0·87	2·10	N.D.	0·60	0·20
4	1·12	1·90	5·40	0·18	0·29	0·90	N.D.	0·06	N.D.
5	0·65	1·88	1·80	0·10	0·51	0·80	N.D.	0·04	1·11
6	1·80	1·56	8·20	0·44	1·00	2·20	N.D.	0·62	0·60
7	1·90	2·33	3·80	0·35	1·11	1·50	0·05	0·52	1·74
8	1·40	4·70	9·00	0·23	1·35	2·40	N.D.	0·28	0·60
9	1·41	8·10	3·20	0·28	2·10	1·50	0·07	0·21	0·08
10	2·43	10·30	7·84	0·36	2·60	1·40	0·02	0·42	0·03
11	0·87	4·20	0·43	0·21	2·00	0·24	0·02	1·32	0·51
12	1·85	7·10	3·20	0·36	1·40	0·27	0·01	0·36	0·01
Mean	1·63	5·26	6·22	0·32	1·46	1·74	0·07	0·46	0·53

Ratio of peak (1 hr.) levels—Penicillin V/Phenethicillin/PA–248 = 1·63/5·26/6·22.
N.D. = Nil detected. = 1·00/3·20/3·80.

Assay Technique

The serum levels were determined by the methods described by Brownlee et al. (1948) with *Sarcina lutea* A.T.C.C. 9341 as the test organism. 'Penassay' seed agar (Difco), pH 6·8, was seeded with a 24-hour culture of *Sarcina lutea* diluted to allow 50% light transmission with a 6500 Å filter on an 'EEL' absorptiometer, to give a final inoculum concentration of 3%. Each assay tray was filled, on a plane table, with 110 ml. of the seeded agar. When the agar set, stainless-steel cylinders (8 mm. diameter) were placed on the surface and filled in a randomised manner with the appropriate standard solutions and sera under examination. After overnight incubation at 28°C, the zone diameters were measured and the concentrations determined by reference to a standard curve.

Preparation of Standard Solutions and Test Sera

The dose/response curves for each penicillin were obtained by plotting the diameter of the zone of inhibition against the logarithm of the dose of each penicillin. Previous experience had shown that, when 6% bovine albumin was employed as diluent, the dose/response curves of all penicillins in this study were parallel. Consequently, the samples of serum were diluted for assay with 6% bovine albumin.

In-vitro Experiments

A two-fold serial dilution tube technique was employed using brain-heart infusion (B.H.I. Difco) as growth medium. In the case of neisseriæ and *Hæmophilus influenzæ*, appropriate media were used in place of B.H.I. Stock solutions of each penicillin were freshly prepared each week and stored at 4°C. All stock solutions were discarded 4 days after preparation. It was ascertained that during this period there was no diminution in potency in the stock solutions.

The inoculum was 0·03 ml. of a 1/100 dilution of an 18-hour culture in B.H.I. into 1·0 ml. of the same medium. For *Neisseria gonorrhœæ* the inoculum was an undiluted culture. Every test was run in duplicate and repeated at least once on a separate occasion. Each series of tests included the Oxford staphylococcus (N.C.T.C. 6571) as control organism. The

TABLE II—SERUM-ANTIBACTERIAL ACTIVITY (FINLAND METHOD) (I.U. per ml.) OF PA–248, PHENETHICILLIN, AND PENICILLIN V FOLLOWING ORAL ADMINISTRATION OF A SINGLE 250 mg. DOSE

Subject no.	Hours after administration								
	1			2			4		
	Penicillin V	Phenethicillin	PA–248	Penicillin V	Phenethicillin	PA–248	Penicillin V	Phenethicillin	PA–248
1	2·30	3·60	2·10	0·44	1·13	1·05	N.D.	0·24	0·17
2	1·30	2·80	3·00	0·90	0·80	0·90	0·09	0·33	0·14
3	1·60	1·30	2·03	0·23	0·45	0·66	N.D.	0·30	0·05
4	1·10	1·00	1·30	0·29	0·17	0·21	N.D.	0·05	N.D.
5	0·44	0·80	0·61	0·08	0·32	0·32	N.D.	0·06	0·39
6	1·35	1·00	1·80	0·38	0·48	0·80	N.D.	0·40	0·20
7	1·40	1·10	1·04	0·29	0·55	0·44	0·05	0·35	0·58
8	1·10	1·60	2·40	0·22	0·63	0·78	N.D.	0·21	0·22
9	1·37	2·30	2·20	0·26	0·70	1·12	0·20	0·07	0·14
10	2·10	3·30	3·80	0·30	0·80	1·12	0·06	0·14	0·14
11	0·75	1·10	0·60	0·19	0·60	0·50	0·06	0·42	0·76
12	1·60	1·90	2·00	0·33	0·50	0·59	0·05	0·12	0·08
Mean	1·37	1·82	1·90	0·33	0·59	0·71	0·04	0·22	0·25

Ratio of peak (1 hr.) values—Penicillin V/Phenethicillin/PA–248 = 1·37/1·82/1·90.
N.D. = Nil detected. = 1·00/1·30/1·40.

TABLE III—ACTUAL AND CALCULATED MEAN SERUM CONCENTRATIONS (μg. per ml.) OF THREE PENICILLINS AT VARIOUS TIMES AFTER ORAL ADMINISTRATION

Penicillin	Hours after administration								
	1			2			4		
	Actual weight (μg.)	Calculated weight (μg.)	Apparent loss (%)	Actual weight (μg.)	Calculated weight (μg.)	Apparent loss (%)	Actual weight (μg.)	Calculated weight (μg.)	Apparent loss (%)
Penicillin V	1·63	0·90	43	0·32	0·22	31	0·07	0·03	57
Phenethicillin	5·26	2·76	47·5	1·46	0·89	39	0·46	0·33	28·3
PA–248	6·22	3·02	51·5	1·74	1·13	38·4	0·53	0·40	24·5

Penicillin V = 1·53 I.U. per μg.
Phenethicillin = 0·66 I.U. per μg.
PA–248 = 0·63 I.U. per μg.
} As determined by biological assay.

TABLE IV—MINIMUM INHIBITORY CONCENTRATIONS OF PENICILLIN G AND THREE ORAL PENICILLINS FOR SENSITIVE AND RESISTANT STRAINS OF *Staph. aureus*

State	Strain	Phage type (group)	Minimum inhibitory concentration (μg. per ml.)			
			Penicillin G	Penicillin V	Phenethicillin	PA–248
Sensitive	Oxford	52 A/79 (I)	0·031	0·031	0·076	0·094
	37	52 A/79 (I)	0·063	0·063	0·063	0·125
	39	52 A/79 (I)	0·031	0·031	0·063	0·125
	48	3c/55/71 (II)	0·031	0·031	0·063	0·125
	49	55 (II)	0·031	0·031	0·063	0·125
	27	187 (III)	0·047	0·047	0·125	0·125
	30	47 (III)	0·031	0·031	0·125	0·063
Resistant	9	52 A/79 (I)	2·70	2·00	0·79	0·60
	14	52 A/79 (I)	4·00	3·00	3·00	0·50
	32	52 A/79 (I)	3·00	1·50	1·00	0·50
	69	80 (I)	6·00	2·00	1·50	0·50
	93	52 A/80 (I)	1·00	0·38	0·38	0·25
	101	180 (I)	1·00	0·75	0·50	0·50
	109	73 (III)	2·00	1·50	0·50	0·50

variation in the minimum inhibitory concentration (M.I.C.) of the four penicillins for this strain did not vary more than one tube throughout the investigation.

In the reading of the results, three complementary methods were employed—namely, turbidity, the production of acid from glucose, and subculture to provide evidence of growth and purity.

Except for a small number of N.C.T.C. and laboratory strains, all organisms used were freshly isolated from clinical material from the General Infirmary at Leeds.

Results

Blood-level Studies

Table I shows that, by weight, PA–248 produces peak serum concentrations which are 3·82 times those produced by penicillin V, while phenethicillin produces levels which are 3·23 times those of penicillin V. The antibacterial activity of the same serum samples was 1·4 times greater in the case of PA–248 than that produced by penicillin V. The antibacterial activity of phenethicillin was shown to be 1·3 times greater than that of penicillin V (table II).

Serum Inactivation

An attempt was made to calculate the degree of inactivation of the three penicillins in vivo. In the experiment summarised in table III, the weight per unit volume of serum was assayed and, in addition, the antibacterial activity of the same samples of serum was assayed in terms of penicillin-G activity. In this way the calculated weight, based on the number of international units per ml., can be compared with the actual weight of penicillin in the blood, and any difference will reflect the degree of serum inactivation. The comparison in table III shows that, at the peak 1-hour level, there is approximately 50% inactivation of all three penicillins.

In-vitro Studies

The minimum inhibitory concentrations of the four penicillins for sensitive and resistant staphylococci, streptococci, *Hæmophilus influenzæ*, and neisseriæ were determined (tables IV and V). All the values quoted in these tables are the mean of two or more replicate experiments.

Penicillin G and penicillin V show an appreciable increase in the M.I.C. with increasing inoculum size of a resistant staphylococcus. This effect is much reduced with phenethicillin and is least with PA–248, suggesting that this latter penicillin is the most resistant of oral penicillins to the action of penicillinase (table VI).

TABLE VI—THE EFFECT OF INOCULUM SIZE (OF *Staph. aureus*—STRAIN 9) ON THE ACTIVITY OF FOUR PENICILLINS.

Dilution factor of culture	Minimum inhibitory concentration (μg. per ml.)			
	Penicillin G	Penicillin V	Phenethicillin	PA–248
1/1000	0·75	0·75	0·75	0·38
1/100	2·70	2·00	0·97	0·60
1/10	64	64	2·00	1·40

The values given are the means of replicate experiments carried out on three separate occasions.

Discussion

Reference has already been made to two methods in general use for assessing the potential value of new antibiotics by serum-level studies. The first of these relies on the determination of the weight of antibiotic per unit volume of serum, while the second depends on the deter-

TABLE V—MINIMUM INHIBITORY CONCENTRATIONS OF PENICILLIN G AND THREE ORAL PENICILLINS FOR STREPTOCOCCI, *H. influenzæ*, AND NEISSERIÆ

Species	Strain	Minimum inhibitory concentration (μg. per ml.)			
		Penicillin G	Penicillin V	Phenethicillin	PA–248
Str. viridans	L 6990	0·031	0·031	0·063	0·063
Str. pneumoniæ	N.C.T.C. 7456	0·016	0·024	0·029	0·031
	L 6007	0·016	0·024	0·024	0·024
	L 6003	0·008	0·016	0·016	0·016
	L 6076	0·016	0·031	0·063	0·031
Str. pyogenes	L 9	2	4	4	4
	L 5995	2	2	4	4
H. influenzæ	N.C.T.C. 4560	1·0	4	12	8
	L W	1·0	16	24	24
	L H	0·5	4	6	8
	L M	1·5	16	24	32
N. gonorrhœæ	L 295	<0·008	0·016	0·031	0·094
	L 5727	<0·008	0·031	0·063	0·125
	L 5715	<0·008	0·031	0·063	0·094
N. meningitidis	N.C.T.C. 8339	0·016	0·063	0·125	0·125
	L	0·031	0·063	0·125	0·25

mination of the antibacterial activity of serum samples in terms of the biological activity of a standard or reference antibiotic. In both the in-vivo findings are correlated with the results of in-vitro studies to give information on the spectrum of the new antibiotic and guidance to the dosage required for its therapeutic application.

Garrod (1960a) suggests that, since allowance has to be made for the difference in sensitivity of a wide variety of organisms, weight concentrations of the antibiotic in serum provide the most useful guide to its therapeutic potentialities. Using these criteria (table I), the peak serum level of PA–248 is approximately 4 times that of penicillin V and 20% greater than that of phenethicillin.

Because, in the in-vitro studies, the M.I.C.s of phenethicillin and PA–248 were 2–4 times greater than those of penicillin V, all three oral penicillins will probably be equally effective against infections caused by sensitive staphylococci.

Against streptococci, the M.I.C.s of all three oral penicillins are roughly equal. Because of the higher blood levels following oral administration of PA–248, this penicillin is likely to be more effective against streptococcal infections than either penicillin V or phenethicillin.

Against gram-negative organisms, penicillin G is the most active, followed by penicillin V, phenethicillin, and PA–248 in that order. These findings are in accord with those of Garrod (1960b).

Against resistant staphylococci, table IV shows that PA–248 is more effective than phenethicillin, which in turn is more active than penicillin V. Since, in addition, PA–248 produces higher blood levels than either of these two penicillins, it may be assumed that PA–248 will be the least likely of the oral penicillins to permit the emergence of resistant staphylococci.

Kunin et al. (1959) have advocated that serum-antibacterial activity should be expressed with reference to a standard antibiotic. In the case of penicillins, this requires estimation of the number of international units of activity of each serum sample with reference to penicillin G. Similar units must, of course, be used to express the values for the minimum inhibitory concentrations. When the results are considered in this way, the peak serum activity, in international units, produced by PA–248 is roughly equal to that of phenethicillin, and 1·4 times that of penicillin V (table II). When the M.I.C.s for sensitive staphylococci are expressed in international units per ml. (figures which can be readily calculated from table IV) all three penicillins are equally effective. Against streptococci, phenethicillin and PA–248 are superior to penicillin V by a factor of 2. In the case of gram-negative organisms the M.I.C.s for the three oral penicillins are approximately equal. (Calculated from table V.)

Expression of the in-vitro results, and results of serum activity levels, in either international units or microgrammes, allows identical conclusions regarding the relative merits of the three oral penicillins.

Since the degree of inactivation in vivo of all three oral penicillins is approximately equal, the above conclusions on their relative effectiveness are not influenced by this factor.

As the relative therapeutic value of penicillin V and phenethicillin is well established, and is in accord with the results of the in-vivo and in-vitro studies described, PA–248 will probably prove the most generally useful oral penicillin in clinical practice.

Summary

Studies with the potassium salt of *a*-phenoxypropyl penicillin (PA–248) show that, after oral administration, PA–248 produces peak serum levels (in μg. per ml.) approximately 4 times as high as those of penicillin V and 20% higher than those of phenethicillin.

Correlation of these relative serum levels with in-vitro results indicates that: (1) the three oral penicillins will be equally effective against sensitive staphylococci; (2) PA–248 will be the most effective of the three oral penicillins against resistant staphylococci; and (3) PA–248 will be the most effective of the three oral penicillins in streptococcal infections.

Attention is drawn to the fact that the three oral penicillins are less effective than penicillin G against gram-negative cocci and bacilli.

The laboratory work has been possible only through the courtesy of Prof. C. L. Oakley, F.R.S., professor of bacteriology, the School of Medicine, Leeds. We should like to express our appreciation of the valuable cooperation of Mr. B. A. Forder, of Pfizer, Ltd., and his staff, in particular Mr. Owen Hughes. It is a pleasure to acknowledge the contribution to the study of the volunteers who took part and of Sister Lipscombe and her staff.

REFERENCES

Brownlee, K. A., Delves, C. S., Dorman, M., Green, C. A., Grenfell, E., Johnson, J. D. A., Smith, N. (1948) *J. gen. Microbiol.* **2**, 40.
Garrod, L. P. (1960a) *Bull. Hyg., Lond.* **35**, 384.
— (1960b) *Brit. med. J.* ii, 1695.
Kunin, C. M., Dornbush, A. C., Finland, M. (1959) *J. clin. Invest.* **38**, 1950.

COMPARATIVE IN-VITRO ACTIVITIES OF FIVE PENICILLINS AGAINST PENICILLINASE-PRODUCING STAPHYLOCOCCI

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THE experiments described here were designed to compare the in-vitro activity of α-phenoxypropyl penicillin (PA-248) against penicillinase-producing staphylococci with the activities of other penicillin derivatives. The penicillins used, in addition to PA-248, were penicillin G, penicillin V, phenethicillin ('Broxil'), and methicillin ('Celbenin'). Eleven strains of penicillinase-producing staphylococci of different phage-types were obtained from clinical material and used as test organisms; two additional strains, numbered 14 and 69, were supplied by Pfizer, Ltd.

Method

Stock solutions of the penicillins, containing 1 mg. per ml., were prepared in 0·01*M* phosphate buffer, pH 6·9. The medium was indicator-serum broth (Stokes 1955), and was distributed in 0·5 ml. volumes in $3 \times {}^{1}/_{2}$ in. aluminium-capped sterile tubes. The final range of penicillin concentrations in the broth extended from 250 μg. per ml. to 1 μg. per ml. Penicillin dilutions were prepared in the phosphate buffer, and 0·5 ml. of a suitable penicillin solution was added to each 0·5 ml. of broth to give the required concentration.

The inocula were prepared from overnight (18-hour) cultures of the staphylococci on meat-digest agar slopes. The growth was washed off with saline, and the suspension standardised photometrically to an optical density of 0·4. Each tube in the

test series was inoculated with 0·02 ml. (from a 50-drop pipette) of a 1/8 dilution of this suspension. The inoculated tubes were incubated overnight at 37°C, and the end-points were then read.

Results

Under the conditions of these tests, seven strains of staphylococci were inhibited by 125 μg. penicillin G per ml., five by 250 μg. per ml., and one was not inhibited even at this level. PA-248 was consistently more inhibitory than penicillin G, but the ratios of their activities differed strikingly with different strains of staphylococci. With two strains the PA-248/penicillin-G activity ratio was about 15/1, whereas with other strains the ratio ranged from 2/1 to 8/1. Dimethoxyphenicillin at 4 μg. per ml. inhibited all the strains.

In another set of experiments with the same organisms, PA-248 was found to be generally more inhibitory than phenethicillin or penicillin V. With two strains the sensitivities to PA-248 and phenethicillin were the same. With the other strains, PA-248 was 2 to 4 times as inhibitory as phenethicillin. Against all strains, PA-248 was more inhibitory than penicillin V, the highest PA-248/penicillin-V activity ratio being 8/1.

These results support the in-vitro findings with staphylococci reported by Williamson et al. (1961) and could be accounted for in part if PA-248 is less sensitive than the other penicillins to the action of staphylococcal penicillinase. The considerable difference in activity ratios from strain to stain, due to the wide fluctuation in sensitivities of the different strains to PA-248, probably requires some additional explanation. In spite of this variability, PA-248 still usually inhibited at lower concentrations than the other compounds tested (except dimethoxyphenicillin), the variation in its activity being towards increased relative effectiveness. As an example, four of the thirteen strains appeared only twice as resistant to PA-248 as to dimethoxyphenicillin.

We wish to thank Messrs. Pfizer, Ltd., for kindly providing the sample PA-248, and technical data on this compound.

REFERENCES

Stokes, E. J. (1955) Clinical Bacteriology; p. 275. London.
Williamson, G. M., Morrison, J. K., Stevens, K. J. (1961) *Lancet*, i, 847.

CLINICAL USE OF A NEW SYNTHETIC PENICILLIN: PA-248

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A NEW synthetic penicillin—α-phenoxypropyl penicillin (PA-248)—was offered for clinical trial some four months ago in order to compare its activity and clinical efficacy with that of other penicillin derivatives—particularly penicillin V. Williamson et al. (1961) found that in vitro PA-248 was more active than penicillin V in a ratio of 8/1 against staphylococci which produced penicillinase, and this has been confirmed by Jackson and Rao (1961).

It seemed possible that PA-248, less sensitive as it is to staphylococcal penicillinase, exhibits differences with different strains of organisms, and it was thought reasonable to ascertain the clinical effect of this substance in both penicillin-sensitive and penicillin-resistant infections.

Clinical Material

The patients had respiratory infections due to coagulase-positive *Staphylococcus aureus*, which was recovered from the sputum in all cases. They had the typical history, symptoms, and signs of a pneumonic inflammatory illness, ranging from segmental consolidation to multilobar abscess formation (see accompanying table).

DATA ON 9 CASES OF RESPIRATORY INFECTION TREATED WITH PA-248

Case no.	Bacteriological findings	Diagnosis	X-ray
1	*Staph. aureus* + *Hæmophilus influenzæ*	Lt. lower lobe pneumonia	Consolidation
2	,,	Suppurative bronchitis; rt. lower and lt. lower lobe bronchiectasis	Bilateral pneumonitis
3	*Staph. aureus* + proteus	Lt. lower lobe pneumonia	Consolidation
4	*Staph. aureus* + *Micrococcus catarrhalis*	Lung abscesses	Bilateral cavitation
5	Penicillin-resistant *Staph. aureus*	Bronchopneumonia and suppurative bronchitis	Bilateral generalised infiltration
6	,,	Pneumonia	Scattered consolidation
7	,,	,,	Consolidation
8	,,	,,	,,
9	,,	,,	,,

Of the 9 cases treated with PA-248, 5 excreted penicillin-resistant organisms. They were compared with a second group of cases treated at the same time which were similar except that in all these cases the organisms were penicillin-sensitive. The first group received PA-248 1 g. daily in four divided doses, and the second group penicillin V 1 g. daily in four divided doses.

Results

Bacteriological clearing of the sputum occurred in all cases in both groups, and from the point of view of clinical efficacy there was no doubt that the patients infected with penicillin-resistant staphylococci benefited no less from treatment with PA-248 than did those infected with penicillin-sensitive organisms.

Radiographic improvement and reduction of elevated temperature, of tachycardia, of erythrocyte-sedimentation rate and of constitutional symptoms and signs were equal in the two groups.

Side-effects (some nausea and occasional dizziness) were observed in the group treated with penicillin V but not in the group treated with PA-248—though the number of cases is far too small in each group or in toto for this observation to have any significance.

Discussion

5 cases of pneumonia due to infection with penicillin-resistant staphylococci resolved clinically, bacteriologically, and constitutionally when treated with the new synthetic penicillin, while infections occasioned by penicillin-sensitive organisms responded as well to this new penicillin as to penicillin V. This work is continuing and more cases are being treated and fully analysed. It is not possible to draw further conclusions at this stage.

Summary

Two groups of patients with respiratory infections were treated—one with α-phenoxypropyl penicillin, and the other with penicillin V.

The response to treatment in the two groups was identical.

α-phenoxypropyl penicillin was effective in 5 cases with penicillin-resistant staphylococci in the sputum.

I thank Messrs. Pfizer, Ltd., for providing the new penicillin and for technical information on it.

REFERENCES

Jackson, F. L., Rao, K. K. (1961) *Lancet*, i, 850.
Williamson, G. M., Morrison, J. K., Stevens, K. J. (1961) *ibid.* p. 847.

A QUANTITATIVE METHOD FOR STUDYING TUMOUR CELLS IN BLOOD

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SINCE the publication of Engell's study in 1955 there has been considerable interest in the isolation of tumour cells from blood. We have been concerned to find a technique that is reproducible, reliable, and quantitative, so that estimates can be made of the numbers of these cells present in the peripheral blood and in the blood draining tumour sites.

Published methods for the isolation of tumour cells from blood depend mainly on lysis or on differential specific gravities.

One lytic method (Malmgren et al. 1958) uses streptolysin to lyse the red blood-cells and the polymorph white blood-cells; tumour cells and lymphocytes are more resistant. The concentration of streptolysin is critical, so that tumour cells can easily be damaged; the cost, moreover, is very high. The specific-gravity methods rely on tumour cells being lighter than erythrocytes and polymorphs. Methods have been described using bovine albumin solutions as the substrate (Roberts et al. 1958) or mixtures of silicones (Seal 1959) to achieve the desired specific gravity. In our hands, however, these methods did not prove reliably quantitative.

The method to be described is based on a different principle. Polymorphs are allowed to ingest iron, and are then removed with a magnet. The red blood-cells are readily lysed by brief exposure to saponin, and the residual cells (lymphocytes and any other blood-cells or tumour cells) are fixed and filtered off on to a 'Millipore'* membrane. 5 ml. of blood can be passed through a single membrane of 47 mm. diameter, and the resultant preparation has an acceptable concentration of cells when viewed microscopically. The membrane is stained with hæmatoxylin and eosin; it is then cleared and mounted in a synthetic resin,† as recommended by Seal (1959). There is little morphological damage to cells by this method.

Cassen et al. (1958) recommended the use of carbonyl iron powder (grade SF) for phagocytosis by polymorphs.

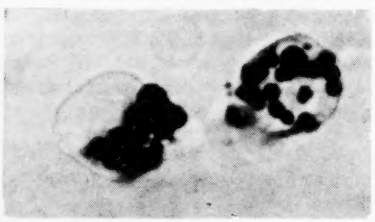

Fig. 1—Unstained film of blood showing two polymorph leucocytes with phagocytosed iron particles.

They advocated coating the particles with gum arabic, but we have found this unnecessary. The grade of fineness (3 μ diameter), however, appears to be critical. Active phagocytosis occurred at 37°C; after 30 minutes of gentle agitation, virtually every polymorph present was found to have ingested several iron spherules (fig. 1). Levine (1956) recommended using an electromagnet for separating such cells, but we have found a good permanent magnet quite satisfactory and more convenient. A magnet is preferred to centrifugation, so as to avoid carrying down tumour cells together with the iron-laden phagocytes.

The choice of anticoagulant is important. We did not use defibrination, for fear of entangling tumour cells in the fibrin skein. Phagocytosis did not occur with citrate or oxalate anticoagulants nor with edetic acid (E.D.T.A.) alone. Heparin, however, was highly satisfactory, and the phagocytic property certainly persists for many hours. If a long delay is unavoidable, results are usually improved by adding a mixture of edetic acid and magnesium chloride to the blood shortly after its collection into heparin. If this is not done, numerous fibrin strands may be deposited when the iron powder is added.

Method

1. Blood is collected into heparin (10 ml. blood and 100 I.U. heparin) and should be processed within a few hours. Edetic-acid/magnesium-chloride mixture is added if blood has to be stored overnight.‡

2. Approximately 100 mg. of carbonyl iron (grade SF) is added, and the container is slowly rotated in the incubator for 30 minutes. Two replicates of 4 or 5 ml. are then processed.

3. To 4 or 5 ml. blood in a shallow glass dish 5 ml. of 0·5% saponin in physiological saline is added and mixed.

4. A strong permanent U-shaped magnet is placed in the glass dish, and the vessel is agitated so that the blood swirls round the poles of the magnet. The magnet is removed and a little more saponin solution is used to wash any free cells back into the container. The magnet is carefully wiped, and the process is repeated several times, until no more iron is removed.

5. When lysis is complete, the fluid is poured into a conical centrifuge tube, the dish is rinsed with a little saponin solution, and the fluid is centrifuged no harder than is necessary to throw down all the cells (3000 r.p.m. for two minutes usually suffices).

6. The supernatant fluid is carefully sucked off, removing the plasma-proteins and free hæmoglobin but not disturbing the deposit.

7. The deposit is resuspended in saline, and decanted into a dish containing 10 ml. of fixative (10% formalin and 10% acetic acid in 50% alcohol, freshly prepared). The centrifuge tube is rinsed twice with extra fixative. Fixation is completed within 2 minutes.

8. The magnetic process is repeated once, to remove any iron particles that escaped the earlier processing and may have been aggregated by centrifugation.

9. The fluid is passed through a millipore filter (type S.M. plain white, 47 mm. diameter, and 5 μ pore size) using suction. The tube is rinsed with fresh fixative and this is also filtered. Suction is continued until the membrane appears quite dry.

10. The membrane is stained for 2 minutes in Ehrlich's acid hæmatoxylin, followed by 20 minutes' washing in water and 5 seconds' differentiation in 1% HCl in 50% alcohol; after a further 5 minutes' washing it is counterstained with 0·5% W.S. eosin for 5 seconds and rinsed again. (Each membrane is stained in a separate glass dish, to avoid accidental transference of cells that may have been dislodged. The stains are filtered before they are used again.)

11. The membrane is placed on blotting-paper to dry the under-surface. Then it is dehydrated in 3 or 4 changes of absolute alcohol (2–3 minutes each).

12. Finally it is cleared in two changes of xylol and mounted in HSR mountant on a 3×2 in. slide.

Application of the Method

Recovery of Added Cells

Tumour cells were found unsatisfactory for these studies, because of the difficulty of preparing uniform suspensions of small numbers of cells to add to blood, and of counting some types of small tumour cells in the final preparations. Defatted pine-pollen grains of approximately 20 μ diameter were found

‡Na_2H_2	edetic acid	1·37 g.
$MgCl_2$	$6H_2O$	0·1 g.
NaCl		0·85 g.
Distilled water		100 ml.

The pH is adjusted to 7·0 with N/10 NaOH. 0·1 ml. of this solution is added to every 1·4 ml. of blood.

* Millipore Filter Corporation, Bedford, Mass., U.S.A.
† HSR (Harleco Synthetic Resin). Hartman-Leddon Co., Philadelphia, Pa., U.S.A.

suitable, for they did not adhere to each other during the processing and were easily distinguishable from blood-cells. A suspension was prepared and samples passed through millipore membranes, the number of grains held back on the filter being counted. Ten samples gave a mean count of 32 with a standard deviation of 11. Further samples of the same suspension were added to 4 ml. of blood, and the whole was treated with iron and saponin, filtered, and stained. Thirteen samples gave a mean count of 33 with a standard deviation of 5. In a second series of ten samples each with another suspension the corresponding counts were 25 (S.D.6) and 31 (S.D.7).

An attempt was made to find out whether tumour cells phagocytose carbonyl iron particles. Six types of mouse tumour were tested, using the cells present in ascitic fluid. Some uptake occurred with three of the six tumours but never in more than 10% of the cells present. With human tumour scrapings, no uptake was seen in ten bronchial carcinomas investigated or in nine bladder, two breast, and two uterine carcinomas. It seems likely that few, if any, tumour cells in a blood sample will be lost during the removal of the iron-laden polymorphs.

Probably, therefore, the method gives quantitative and reproducible results.

Peripheral-vein Blood

160 samples of blood were examined from patients with and without malignant neoplasms. The membranes were

Fig. 2—Clump of cells, probably derived from a tumour, found in peripheral blood of a patient with a malignant neoplasm of the renal pelvis. (Hæmatoxylin and eosin.)

repeatedly examined, and the presence of suspected tumour cells was recorded without knowledge of the origin of the specimen. Suspected cells were classed as " highly suggestive " or " suggestive " (fig. 2).

Of 78 samples from patients classed as having non-neoplastic diseases, " suggestive " cells were found in 1 of 2 samples from the same patient. This patient was re-examined 9 months later, and no other evidence of neoplasm was found, although similar cells were again found in a blood sample. No " suggestive " cells were discovered in 15 samples from healthy individuals.

54 samples were examined from 36 patients with bronchial carcinomas (in 29 of these, histological evidence was available).

Of 29 samples of 8 ml., " highly suggestive " cells were recorded in 2 and " suggestive " cells in 3. In 25 samples of 4 ml. the corresponding findings were 2 and 2. " Highly suggestive " cells were found in only 3 (8%) of the 36 patients. There was a slight indication that the presence of suspected tumour cells in peripheral blood might be related to the presence of metastases; " highly suggestive " or " suggestive " cells were seen in 7 of 38 samples from patients with evidence of metastases and in 2 of 16 from those without.

Of 13 samples from patients with advanced malignant neoplasms elsewhere than the lung, " highly suggestive " cells were seen in 1 and " suggestive " cells in 1.

Blood from Veins Draining the Tumour Site

Blood was obtained from the pulmonary vein at thoracotomy in 10 cases; " highly suggestive " cells were seen in 3 (30%) and " suggestive " in 1.

Comment

Considerable difficulty was experienced in deciding whether unusual-looking cells were likely to have come from a tumour. The variety of unusual, but non-neoplastic, cells found in preparation of relatively large volumes of blood has been described by Sandberg et al. (1959) and Alexander and Spriggs (1960). Unfortunately, some reports of the alleged frequency of tumour cells in blood appear to have been made before this source of error was fully appreciated. We have studied the appearance of cells from bronchial and other carcinomas in preparations obtained by recovering tumour scrapings on membranes. Bone-marrow was processed in the same way as blood, and the appearance of normal marrow cells was studied on the membranes. The identification of these cells on membranes was facilitated by comparison with smears on slides stained by hæmatoxylin and eosin and by the May-Grünwald method. Even with this experience we prefer at present to classify cells as probably from a tumour, rather than as definite tumour cells.

Our identification is to some extent validated by the fact that " suggestive " cells were reported, without knowledge of the source of the specimen, in only 1 of 78 samples from patients with no evidence of neoplasm, and by the slight correlation with the presence of metastases in those with neoplasms. Nevertheless, if only a few unusual cells are seen on a membrane, we cannot at present assert that they have originated from a tumour, unless, as in the case of a melanoma, the cells have clearly identifying characteristics.

More knowledge of the variety and morphology of unusual cells in blood is required before tumour cells can be identified with certainty.

Summary

A method is described for removing erythrocytes and polymorph leucocytes from blood so that tumour cells can be identified and counted among the remaining cellular elements.

The method is simple and is apparently reliable and quantitative; but the identification of unusual cells as having originated from tumours is at present difficult. " Highly suggestive " cells were found in 4 or 8 ml. samples of peripheral blood in 3 (8%) of 36 patients with bronchial carinoma, and of pulmonary-vein blood in 3 (30%) of 10. But " suggestive " cells were also recorded in 1 of 78 samples from patients without other evidence of neoplasm.

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REFERENCES

Alexander, R. F., Spriggs, A. I. (1960) *J. clin. Path.* **13,** 414.
Cassen, B., Hitt, J., Hays, E. F. (1958) *J. Lab. clin. Med.* **52,** 778.
Engell, H. C. (1955) *Acta chir. scand.* suppl. 201.
Levine, S. (1956) *Science,* **123,** 185.
Malmgren, R. A., Pruitt, J. C., Del Vecchio, P. R., Potter, J. F. (1958) *J. nat. Cancer Inst.* **20,** 1203.
Roberts, S., Watne, A., McGrath, R., McGrew, E., Cole, W. H. (1958) *Arch. Surg.* **76,** 334.
Sandberg, A. A., Moore, G. E., Schubarg, J. R. (1959) *J. nat. Cancer Inst.* **22,** 555.
Seal, S. H. (1959) *Cancer, Philad.* **12,** 590.

AN OUTBREAK OF HUMAN INFECTION DUE TO SALMONELLA TYPHIMURIUM PHAGE-TYPE 20a ASSOCIATED WITH INFECTION IN CALVES

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HUMAN outbreaks of salmonella food-poisoning due to infected beef or milk have been fairly common in the past and have usually been caused by *Salmonella dublin*, but few outbreaks associated with calf meat have been recorded. Buchanan and Bevan (1939) reported an *S. typhimurium* outbreak due to infected veal, and more recently two outbreaks have been reported from Sweden. Lundbeck et al. (1955) described an outbreak of food-poisoning due to *S. typhimurium*, comprising 8845 cases with at least 90 deaths, which was associated with infection in pigs and calves. A second outbreak, described by Kallings et al. (1959), was associated with imported boneless veal. About 500 cases were due to *S. typhimurium* and 7 to *S. bovis-morbificans*; in 2 cases there was a double infection with these organisms.

An outbreak of *S. typhimurium* infection in South-East England, associated with salmonellosis in calves derived from one calf-collecting centre, is described here.

The Outbreak

Between July and October, 1958, 55 incidents * due to *S. typhimurium* phage-type 20a were reported, the majority in the second half of August and the first half of September. None was reported after the end of October.

In 17 incidents the patients were Jews—a fact which suggested kosher meat as a possible source of infection. The number of incidents in each week is shown in fig. 1, the number affecting orthodox Jews being indicated by the shaded area.

The 55 incidents consisted of 43 sporadic cases and twelve outbreaks, the total number of cases being 90. The incidents occurred mainly in London and Brighton and the area between, but also in Oxford. 2 incidents occurred in Manchester, 1 in Southampton, and 1 in Chippenham (fig. 2).

Clinical Features

In only 2 incidents could the incubation period be determined. In one outbreak of 7 cases, symptoms developed twenty-four hours after a common meal. In another 14 cases, 4 patients had symptoms forty-eight hours, 3 seventy-two hours, and 1 eighty-four hours after a common meal. 5 of the 14 cases in this outbreak were secondary, and in 1 the date of onset of symptoms was not known.

There were 42 cases in males and 42 in females; in 6 the sex was not recorded. In 56 out of the 90 the ages of the patients were known. 40 patients (72%) were under 20 years of age, and 22 (39%) under 5, so the highest incidence was in the young.

Clinical information was collected from 56 of the patients. There was 1 death in a woman. The vehicle of infection in this case was not known. A boy, aged 15, had severe abdominal pain with diarrhœa. Appendicectomy was performed, and an inflamed appendix was removed. Two weeks later he had a non-suppurative arthritis of his left knee and right shoulder joints, and *S. typhimurium* phage-type 20a was then isolated from his stools. 3 young men suffering from severe abdominal pain underwent appendicectomy, and were later found to have enteritis due to phage-type 20a. A child aged 5 years was admitted to hospital with convulsions. A woman aged 57 had auricular fibrillation during her attack of enteritis. The cardiac rhythm became regular when the patient recovered from the infection. 50 of the 56 cases are known to have had diarrhœa; but in some fever and malaise marked the onset of the illness and diarrhœa did not develop until twenty-four to forty-eight hours later. In 19 cases abdominal pain was a prominent feature of the illness. No search was made for symptomless excretors in any incident.

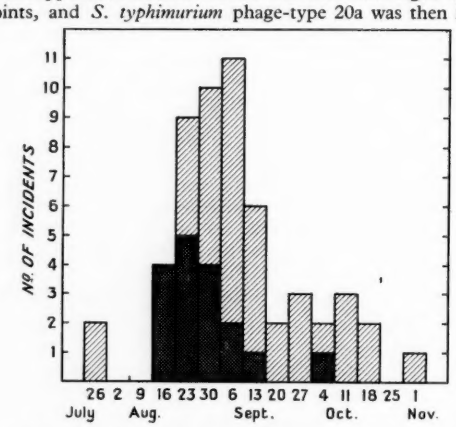

Fig. 1—Weekly incidence of food-poisoning caused by *S. typhimurium* phage-type 20a, July-November, 1958.

Infection in Calves

Early in the outbreak, six cultures of *S. typhimurium* isolated from sick calves on a farm near Chelmsford proved to be phage-type 20a. The calves had all been purchased from a collecting centre near Oxford, which also sold animals to abattoirs in Brighton, London, Oxford, and Salisbury (fig. 2).

Because the same phage-type was isolated from patients and

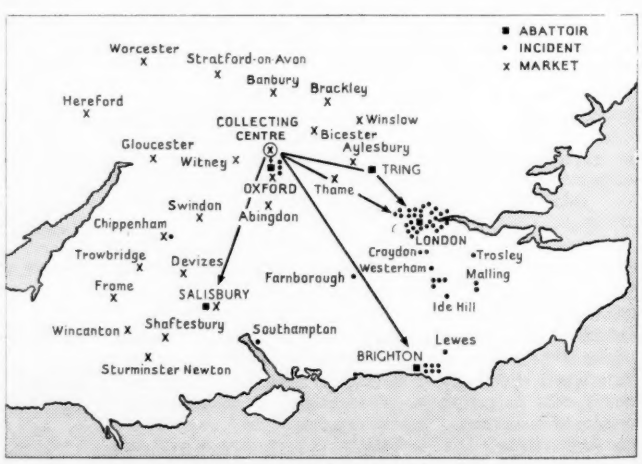

Fig. 2—Distribution of incidents of food-poisoning.

* In this paper, an outbreak means 2 or more related cases, and a sporadic case means a single case not apparently associated with other cases. "Incident" is used to describe either an outbreak or a sporadic case.

from calves, investigations were begun to determine whether calves might be the source of human infection.

Suspected Foods

If veal or calf products had been eaten by a patient within three days, or had been in the house within a period of seven days, before the onset of illness, a direct causal association was considered probable. An indirect association was considered probable if, within such a seven-day period, the household had obtained other meats from shops which at the time of purchase were handling calf meat from a source known to be infected. In no instance was it possible to visit an infected household early enough to obtain samples of the suspected meat, and the organism was never isolated from a suspected foodstuff.

Table I shows the findings. Of a total of 33 incidents involving calf meat, 18 were associated with the consumption of it, 4 occurred in persons handling it, and 11 were indirectly associated with it. One outbreak of 14 cases was due to a meal of cold poultry and salad, but investigations revealed no connection with, or any possible mode of contamination by, calf meat. 2 incidents were thought to be due to hospital cross-infection; in 9 the source of infection was not found. 10 were not investigated; 1 of these was a family outbreak of 3 cases, and the remaining 9 were sporadic.

Thus, though the evidence incriminating calf meat is circumstantial, the meat was the most probable vehicle of infection in at least three-fifths of the incidents.

The Calf-collecting Centre

In 26 of the 33 incidents associated with veal or calf products, the calves had been purchased from a single collecting centre

TABLE I—POSSIBLE SOURCES OF INFECTION

Possible source	No. of incidents
Veal	8
Calf liver	6
Calf tongue	1
Veal-and-ham pie	3
Other meat (possibly contaminated by calf meat)	11
Poultry (mode of infection unknown)	1
Hospital cross-infections	2
Persons handling veal	4
Unknown but fully investigated	9
Not investigated	10
Total incidents	55

near Oxford. This centre had also supplied the calves mentioned previously which developed enteritis due to *S. typhimurium* phage-type 20a. The calves were purchased by the centre from numerous markets, mainly in the West of England, and were sold either to farmers for rearing or to the abattoirs at Oxford, London, Brighton, and Salisbury. They were kept at the centre for varying periods but usually for less than twenty-four hours. It is particularly relevant, however, that the calves for slaughter on Sundays and Mondays might have been purchased on any day after the preceding Wednesday, and were therefore kept together at the collecting centre for between two and five days. At Oxford, London, and Brighton abattoirs, slaughtering was carried out mainly on Sundays and Mondays. At Salisbury abattoir slaughtering was done on Thursdays only, the calves being purchased from markets the previous day.

The collecting centre was investigated, and there were clearly many possibilities of cross-infection, particularly in the pens holding calves destined for the two London abattoirs. One hundred and thirty-three swabs of material in the calf pens were examined, and *S. typhimurium* phage-type 20a was isolated from dust from a ledge on the wall of one pen. None of the specimens from the floor was positive, probably because the pens were frequently sprayed with disinfectant. Rectal swabs of 544 calves already in, or arriving at, the centre were taken on various days of the week, and one of these yielded *S. typhimurium* phage-type 20a. The market and the farm of origin of this calf were investigated with negative results.

Calves were examined at three markets in the West Country in September and October, and though this gave no lead to the source of *S. typhimurium* phage-type 20a, it indicated the rate of salmonella infections in calves. *S. typhimurium* of various phage types was isolated on six occasions (0·5%) from rectal swabs of 1127 calves. 4 of these infected calves had come to market from calf dealers and 2 direct from farms. As most of the 1127 calves examined must have come direct from farms, the mean infection-rate of calves on farms in the area investigated was probably less than 0·5%.

TABLE II—EXAMINATION OF RECTAL AND CÆCAL SWABS OF CALVES AT 2 LONDON KOSHER ABATTOIRS

Abattoir	Day	No. of calves examined	No. positive and organism isolated	Positive (%)	*S. typhimurium* 20a (%)
Calves from Oxford collecting centre:					
A	Monday	133	12 *S. typhimurium* 20a 43 *S. typhimurium* 2c 1 *S. typhimurium* 2 2 *S. typhimurium* untypable 1 *S. dublin*	35·6	12·7
B	Sunday and Monday	72	14 *S. typhimurium* 20a		
A	Tuesday	156	1 *S. dublin*	0·6	Nil
B	Tuesday	8	Nil		
Calves from collecting centres other than Oxford:					
A	Monday	76	2 *S. typhimurium* 2c 1 *S. binza*	3·9	Nil
A	Tuesday	52	2 *S. typhimurium* 2c	3·0	Nil
B	Wednesday	14	Nil		

The Abattoirs

Most of the bacteriological investigations were carried out in two London kosher abattoirs between October and November, 1958. As table II shows, all the isolations of *S. typhimurium* phage-type 20a were from swabs taken on Sundays and Mondays. At Salisbury abattoir, which slaughtered on Thursdays, rectal swabs from a total of 120 calves were taken on four separate visits and were all negative.

Rectal swabs of calves taken after slaughter, but before evisceration, were unlikely to be cross-contaminated, and these were mainly used. Swabs of cæcal contents were also collected at one London abattoir. These were taken by incising the wall of the cæcum, after evisceration, with a scalpel and then inserting the cotton-wool swab. Between each operation the scalpel was wiped clean with sterile wool and placed in 70% alcohol for at least five minutes.

Specimens from a total of 205 calves were collected at the two London abattoirs on Sundays and Mondays, and *S. typhimurium* phage-type 20a was isolated from 26 (12·7%) of the animals. 164 calves were examined on Tuesdays and Wednesdays, but type 20a was not found. A further 142 calves from collecting centres other than Oxford were also examined with negative results. Thus, the infection-rate of calves was highest on Sundays and Mondays—that is, in those animals kept together longest at the collecting centre.

This build-up of infection between market and abattoir was also shown by considering all types of salmonellæ isolated during this study (table II). The mean infection-rate among calves on the farms has been estimated at less than 0·5%. In contrast, in calves slaughtered at the two London abattoirs on Sundays and Mondays—that is, after they had been kept

TABLE III—EXAMINATION OF CALF PRODUCTS AT A LONDON ABATTOIR B AND ONE BUTCHER'S SHOP

Place	Specimen	No. examined	No. positive
Butcher's shop	Calf palates	84	8 *S. typhimurium* 20a 1 *S. bredeney*
Butcher's shop	Calf skin	16	1 *S. bredeney*
Butcher's shop	Veal	16	Nil
Abattoir B	Veal	32	Nil
Butcher's shop	Calf liver	6	Nil
Abattoir B	Calf liver	52	Nil
Abattoir B	Calf spleen	56	1 *S. typhimurium* 20a
Abattoir B	Calf mesenteric glands	52	4 *S. typhimurium* 20a
Total specimens examined		314	13 *S. typhimurium* 20a 2 *S. bredeney*

together for two to five days at the collecting centre—the infection-rate was 35·6%. In those slaughtered on Tuesdays—that is, kept together at the collecting centre for a few hours only—it was 0·6%. Calves coming from collecting centres other than Oxford had a lower infection-rate.

Though the original source of infection was not found, the high rate of infection in calves at slaughter was probably due to cross-infection of the animals herded together for two to five days at the collecting centre.

Investigations in a Butcher's Shop

Investigations were made at a butcher's shop, supplied by one of the London abattoirs, with which 3 human incidents of salmonella infection were associated.

Initially, calves' palates were chosen for sampling because these were identifiable with a particular calf, the identification number being fixed to the ear. The palates were collected by the butcher as he skinned the head. Table III shows that, of 84 such specimens obtained, 8 yielded *S. typhimurium* phage-type 20a and 1 *S. bredeney*. *S. bredeney* was isolated also from 1 out of 16 specimens of calves' skin.

The palates were contaminated from the skin of the head of the animals during collection, and it is interesting to record that all samples that yielded type 20a came from animals slaughtered on Sundays or Mondays—that is, from calves which had been held from two to five days at the collecting centre. No other positive specimens were obtained from the butcher's shop. The results of examinations, other than of fæcal swabs, from one of the London abattoirs, and the results from the butcher's shop, are shown in table III. No positive specimens were obtained from veal or calves' liver, but 5 were obtained from mesenteric glands and spleen. These are not used for human consumption, however, the spleen going to the butcher's shop where it is sold as dog meat.

Possible Channels of Infection

The manner of slaughter of the calves is unlikely to have much effect on the spread of salmonella organisms in the slaughterhouse, but the method used to dress the carcasses is likely to have considerable effect. The carcass is inflated with compressed air through a metal nozzle introduced beneath the skin of the abdominal wall. This strips the skin from the underlying fascia and makes the veal look more attractive by giving it a glistening appearance. The metal nozzles are usually far from clean and often drop to the abattoir floor. Contamination of the nozzle seems inevitable, and when this takes place organisms are probably blown from it over the surface of the carcass. Such contamination, however, is probably not heavy.

The carcass is then skinned, and the feet and head are cut off and allowed to drop to the floor. In the butcher's shop the skin of the head has been found to be contaminated with salmonellæ, and this contamination most probably takes place on the floor of the abattoir.

The viscera are next removed, usually without any soiling of the meat by fæces, but this depends a great deal on the skill of the slaughterman. If he is unskilled, he may puncture the gut of perhaps 5% of carcasses, with resulting fæcal contamination. Skilled slaughtermen probably puncture the gut in less than 1% of the carcasses. Veal is rather sticky, and this adds to the difficulties of removing any contamination. Contamination of carcasses may also occur from the slaughterman's hands or knives, or from wiping them with a wet cloth to remove blood-stains and dirt. Thus, there are considerable opportunities for surface contamination of veal. No information was obtained which would imply that the animals had bacteræmia when slaughtered. All the veal examined came from calves 2 to 3 months old, and these animals are less liable to severe salmonella infections than those of 2 to 3 weeks. No deaths or illness in animals at the collecting centre or abattoirs were reported, but this information is unlikely to be reliable. The possibility cannot be excluded, therefore, that sometimes a calf with septicæmia may have been slaughtered.

Transport from abattoir to shop is by road. Carcasses are supposed to hang in the van. Plucks (liver, spleen, lungs, and heart), heads, and feet are carried in large wire-mesh baskets on the floor of the van. Cross-contamination from heads and feet to plucks or carcasses which may be laid on the floor might well occur.

In the butcher's shop there are considerable differences between the methods of kosher and non-kosher handling. In the non-kosher trade, the meat is often in cold store for periods up to a week, and on reaching the shop the veal is jointed or cut into fillets and sold with little handling. The same applies to the heart, liver, and tongues. Most veal pies are manufactured from meat from calves 1 to 2 days old, and similar veal is often used in the manufacture of pork sausages.

In the kosher trade, the turnover of meat is more rapid, most being sold by the retailer within two to four days of slaughter. The kosher butcher handles meat to a considerable extent because he has to remove the major blood-vessels for his customers. Removal of the blood-vessels involves cutting into the meat with a knife, a process which may implant organisms into the meat. Before sale, the meat is sprinkled with salt and allowed to stand for an hour and then washed in water. Liver cannot be treated in this way, and is lightly grilled until the surface is brown. This is usually done by the housewife, and the liver may then be made into liver pâté without further cooking. Salmonella organisms in the centre of the liver may not be killed by the limited amount of heat employed. Similarly, veal in general tends to be eaten undercooked, and organisms in the centre may escape destruction. Even though organisms contaminating the surface of the meat are killed by cooking, the housewife's hands may transfer bacteria to other food. She may contaminate utensils and the environment and may also infect herself, and thus in one or more of several possible ways start a family outbreak of food-poisoning.

Laboratory Investigations

Isolation of Salmonellæ

Swabs were cultured overnight at 37°C in selenite F medium. Specimens of meat were first held in boiling water for three seconds, in order to destroy organisms contaminating the outside, before being cut up with a sterile knife. They were then cultured overnight at 37°C in selenite F medium. Sub-cultures from selenite F were made on to deoxycholate-citrate-agar plates which were then incubated overnight.

Next morning, non-lactose-fermenting colonies were picked and tested with polyvalent salmonella O serum by slide agglutination. Colonies giving a positive reaction were sub-cultured into Todd-Hewitt broth, which was then incubated until the opacity was approximately equal to 5×10^8 organisms per ml. These broth cultures were then formolised to provide suspensions suitable for tube-agglutination tests using factor-specific diagnostic sera prepared in the standards laboratory, Colindale.

Phage-typing

The phage-typing of *S. typhimurium* was carried out by the established technique (Anderson and Williams 1956, Callow 1959). Under optimal conditions, the results were obtained within four to six hours of receipt of the culture. Though most cultures were received on Dorset egg-slopes, a portion of the original broth culture of non-lactose-fermenting colonies picked from selective media was often used directly for phage-typing. This resulted in a saving of twenty-four hours. Very few of these broth cultures proved to be contaminated with other bacteria.

Discussion

The outbreak described here shows that calves infected with *S. typhimurium* may be an important source of human food-poisoning, especially when they are kept together in large numbers for long periods before slaughter. The build-up of infection between the farm and the abattoir has been demonstrated also in pigs by Galton et al. (1954). McDonagh and Smith (1958) showed that cross-infection took place among pigs held in an abattoir lairage, and found that human salmonella infections in the district were closely related to the abattoir findings.

The rate of salmonella infection of calves and other animals at abattoirs is clearly related to the mixing of the animals in markets, transport wagons, collecting centres, and lairages, and the length of time taken to bring them from the farms to the slaughter hall. It may be related also to the occurrence of epizootics among the calves or other animals with which they are in contact in the areas served by the different collecting centres and abattoirs.

The ultimate source of infection may be contaminated animal feeding stuffs (Ministry of Health 1959), though it is probable that calves on farms are infected, before weaning, by adult cows or by other animals receiving artificial foods. Field (1948) found that salmonellæ were carried by cattle and that calves could become infected by carrier cows, so it is probable that some outbreaks of salmonellosis in calves may arise from such carriers.

The proportion of calves infected with salmonellæ varies in different places and at different times, but it may be greater in abattoirs than is generally realised. Pullinger (1950) in South Africa found 3% of intestines of apparently healthy calves to be infected with salmonellæ at the time of slaughter. Lundbeck et al. (1955), investigating an outbreak of *S. typhimurium* infection in Sweden, examined the lymph-nodes of calves at one abattoir and isolated the organism from between 0 and 13·6% of the specimens on different days. Further examination of calves from the collecting centre implicated in the outbreak described in this paper showed a considerable drop in the rate of infection. These examinations were carried out at the London abattoir "A" on five Mondays between April and July, 1959. Of one hundred and seventy-one rectal swabs, only four (2·3%) contained salmonellæ, compared with 35·6% six months before (table II); and *S. typhimurium* phage-type 20a was not found. In calves arriving at this abattoir from other collecting centres the percentage had risen from 3·9% (table II) to 13·9% (28 out of 202) in the same six months. One of these specimens contained *S. typhimurium* phage-type 20a.

The account of this outbreak shows how phage-typing helped in a number of ways to clarify the epidemiology of *S. typhimurium* infections. Primarily, it linked up a series of incidents mostly scattered around Greater London and the Home Counties, but represented in places as widely separated as Manchester and Brighton. The precision of this identification will be appreciated more fully when it is realised that the outbreak lasted for more than four months and provided a total of only 90 cases in a population of about 17 million. The type 20a cases constituted roughly 17% of all *S. typhimurium* infections encountered during the same period in the same area. Without the guidance of phage-typing it would have been almost impossible to connect the cases with each other.

Secondly, the routine phage-typing of cultures of *S. typhimurium* of animal origin on a wide scale (Anderson 1960) resulted in the identification of six strains isolated from sick calves as type 20a. This provided the clue that led from the farm to the collecting centre where the calves had been bought, and thence to abattoirs where the same type was isolated from slaughtered animals. Thus, phage-typing acted as a guide throughout these investigations. The method is valuable, not only to veterinary workers, who are enabled to clarify the epizootiology of infected livestock, but also to medical workers, because it provides clues to the sources of outbreaks of human infection.

Type 20a of *S. typhimurium* was originally identified in 1946. In the original phage-typing scheme of Felix and Callow (1943, 1951) and Felix (1956) this type was designated 2d. In the revised scheme now in use (Callow 1959) the designation has been changed to 20a. Until the present outbreak, about one hundred and ten cultures of the type had been examined in the Central Enteric Reference Laboratory. The type was first found in an outbreak in Essex in 1946. This epidemic was at the time suspected to be due to corned beef, and type 20a was isolated from samples of this material in three different butchers' shops. Later investigations, however, showed that the corned beef had been contaminated after the cans were opened, and that the organism came from a slaughterhouse that supplied all the shops implicated in the epidemic. The outbreak was large and covered a wide area, but the meat responsible for the infection was not identified. In the light of our recent findings, the Essex outbreak may have had a similar origin to that of the outbreak we describe here.

Between 1946 and 1955 only seven strains of phage-type 20a were encountered. In 1955, however, a hotel outbreak of about 15 cases due to this type occurred in Bournemouth. It was believed to have been caused by infected beef, but, although the organism was isolated from suspected beef, the source of this contamination was not traced. During the same year there was an epidemic of similar size in Worcester and another in Leicester. Most cases encountered between 1947 and 1958 came from the Midlands, South Wales, and the London area, and—apart from those already mentioned—there were at least four smaller outbreaks, in none of which was it possible to trace the source of infection.

Of the one hundred and ten cultures of type 20a encountered before the present outbreak, therefore, at least seventy-two were isolated in nine epidemics. The incidence of *S. typhimurium* infections is so high, and the cases are usually so scattered throughout the general population, that it is relatively rarely that so great a proportion of cultures of a single type can be assigned to distinct outbreaks. The type of material that commonly carries type 20a may be one which predisposes, either by its mode of consumption or by its special opportunities for contaminating other material, to infections that occur in groups of considerable size. Perhaps the principal vector of the type is the calf, but whether 20a has a special ecological relationship with this animal is not yet clear. Since the outbreak described here, we have had only one culture of this type from calves, but intensive investigations of these animals is no longer in progress in the areas concerned. On the other hand, a few human cases still occur from time to time in the areas previously implicated—mainly in Greater London—which suggests that infective foci in animals are still active.

Though the cause of the outbreak was identified beyond reasonable doubt, the details of some of the links in the chain of infection are still lacking. It is hoped that further work will provide these and so facilitate the control of this common disease.

Summary

Between July and October, 1958, 55 separate food-poisoning incidents, comprising 90 cases due to *Salmonella typhimurium* phage-type 20a, were reported in South-East England. There was 1 death. Investigations were directed to calf meat, after the isolation of the same organism from an outbreak of enteritis in calves. Though not conclusive, the evidence strongly suggested calf meat as the vehicle of infection in at least three-fifths of the incidents. Examina-

tions at the abattoirs concerned showed that up to 12·7% of rectal swabs of apparently healthy calves yielded *S. tyhpimurium* phage-type 20a, and the same organism was isolated from 9·5% of specimens of calves' palates from one butcher's shop.

The original source of infection of the calves was not found, but cross-infection during a period of up to five days which the animals spent herded together at a collecting centre probably explains the high isolation-rate in the abattoir.

The investigation demonstrates the value of phage-typing in the study of the epidemiology of *S. typhimurium* infections.

We are indebted to the medical officers of health, directors of public-health laboratories, hospital medical officers, general practitioners, and veterinary officers in Hampshire, Kent, London, Middlesex, Oxfordshire, Surrey, Sussex, and Wiltshire who assisted in the field investigations.

REFERENCES

Anderson, E. S. (1960) *Roy. Soc. Hlth J.* **80**, 260
— Williams, R. E. O. (1956) *J. clin. Path.* **9**, 94.
Buchanan, G., Bevan, C. de V. (1939) *S. Afr. J. med. Sci.* **4**, 111.
Callow, B. R. (1959) *J. Hyg., Camb.* **57**, 346.
Felix, A. (1956) *J. gen. Microbiol.* **14**, 208.
— Callow, B. R. (1943) *Brit. med. J.* ii, 127.
— — (1951) *Lancet*, ii, 10.
Field, H. I. (1948) *Vet. J.* **104**, 251, 294, 323.
Galton, M. M., Smith, W. V., McElrath, H. B., Hardy, A. B. (1954) *J. infect. Dis.* **95**, 236.
Kallings, L. O., Laurell, A.-B., Zetterberg, B. (1959) *Acta path. microbiol. scand.* **45**, 347.
Lundbeck, H., Plazikowski, U., Silverstople, L. (1955) *J. appl. Bact.* **18**, 535.
McDonagh, V. P., Smith, H. G. (1958) *J. Hyg., Camb.* **56**, 271.
Ministry of Health (1959) *Mon. Bull. Minist. Hlth Lab. Serv.* **18**, 26.
Pullinger, E. J. (1950) *J. S. Afr. vet. med. Ass.* **21**, 58.

OPERATION FOR RECTAL PROLAPSE
USING STAINLESS STEEL RING

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IT is nearly seventy years since, according to Lenormant (1903), Thiersch in 1891 described at a medical congress at Halle the operation associated with his name. This operation was the insertion of a silver-wire ligature subcutaneously around the anus to control rectal prolapse. Silver wire was not ideal and many other materials have been used since; these have included silk thread, fascia lata, tendon, rubber tubing, hernial sac, nylon tape, and stainless-steel wire; but none was satisfactory and there has been a return to the use of silver wire. The operation, which had fallen into disuse, was revived by Gabriel (1948), and is essentially the same as that practised by Thiersch seventy years ago. Later, Gabriel (1953) gave an excellent account of the technique, indications, and results. The aims are:

1. To narrow the anal orifice and to control the rectal prolapse.
2. To shorten the fibres of the external sphincter which have been overstretched and are atonic. This allows a more effective contraction of the sphincter, and may restore control of the passage of firm fæces, even if the patient remains incontinent of fluid fæces and flatus.

The operation is indicated:

1. In patients with a small prolapse, and atonic sphincters.
2. In patients with larger degrees of prolapse, unsuitable for major surgery.
3. As a supplementary operation in patients who have undergone abdominal repair for rectal prolapse, whose sphincter tone fails to recover.
4. In patients, usually elderly, with atonic sphincters and incontinence.
5. In patients with incontinence due to divided sphincters (usually after operations for fistula-in-ano).

The complications of the operation using silver wire are: (1) postoperative sepsis; (2) presence of the "twist" or knot, which may cause discomfort or ulcerate through the skin; and (3) the liability of the wire to fracture. A device of non-toxic stainless steel (British Standard En 58J) has therefore been developed.

The Device and its Use

The device takes the form of a hollow needle having a diameter of $^1/_{10}$ in., its length curving through $^5/_8$ of a circle $1^3/_{16}$ in. in diameter. Into this slides a closefitting solid stilette, which is $^1/_2$ in. longer than the needle. The stilette can be made to travel through the lumen of the needle until the point of the stilette enters about $^3/_4$ in. into the tail of the tube, thus forming a complete ring. The stilette moves within the tube with considerable friction and there is no tendency for it to slip out of position (fig. 1*a-c*). The device is introduced with a special forceps with straight handles and with a circular notch cut into the jaws.

The assistant uses a pair of holding forceps which has similar jaws set at an angle to the shanks, which are curved on the flat, so that his hands are not in the operating field.

Before operation the bowel is cleared with enemata or washouts. Intestinal chemotherapy or antibiotics are not necessary.

Either general anæsthesia or caudal block may be used, and the operation is carried out with the patient in the lithotomy position. Any residual fæces in the rectum are evacuated digitally and the perineum is washed with 'Savlon' or 'Cetavlon' (cetrimide). A circumferential nylon ligature is inserted subcutaneously about the anus

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(*a*) (*b*) (*c*)

Fig. 1—The stainless-steel ring.

(*a*) Stilette and needle separated; (*b*) stilette about to pass into hind-end of needle; (*c*) ring assembled, with stilette lying symmetrically within each end of needle. (A mark on stilette shows when this position has been reached.)

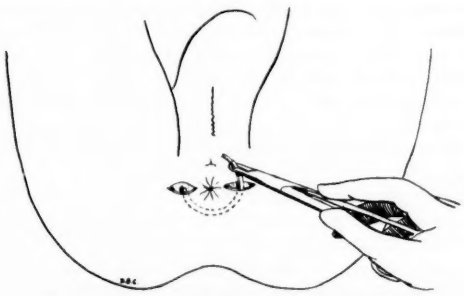

Fig. 2—Introduction of hollow needle and stilette.

and tied firmly: the ends are left about 1 in. long. The operation field is now sterilised with suitable agents, and sterile towels and leggings applied. A formal aseptic operation in a sterile field can now take place.

Two small horizontal incisions $^3/_4$ in. long are made on each side of the anus, and deepened into the ischiorectal fossæ. The device, assembled so that the points are lying flush together, is passed posteriorly about the anus taking a wide sweep on as deep a plane as possible to emerge deeply in the right-hand incision (fig. 2).

The hollow needle is grasped near its hind end by an assistant using the holding forceps which carry his hands away from the operating site.

The stilette is now pushed through the hollow needle by pressure on its hind end, and the pointed end can be picked up in the right-hand incision and passed forwards through the perineal body to emerge in the depths of the left-hand incision (fig. 3).

If the point of the stilette is not seen, it can be found easily by cutting down on it with a fine knife. It is then guided easily into the hollow needle and passed onwards to a point specially marked on the stilette. This ensures that an equal length of stilette lies within each end of the hollow needle. Some difficulty may be experienced passing the stilette forwards through the perineal body, which in these patients may be attenuated, only a thin rectovaginal septum remaining.

It is important not to allow the point of the stilette to pierce the anal canal, and to help prevent this the assistant should thrust forwards the hollow needle, " gathering " the anal canal into its curve.

An alternative method is to introduce both parts of the ring separately, the hollow needle being inserted posteriorly in the manner already described, after which the stilette may be passed through the rectovaginal septum independently. It is quite easily guided into the one end of the hollow needle, and then " shunted " backwards into the other end.

Finally, the skin is closed with clips, and the encircling ligature is cut out.

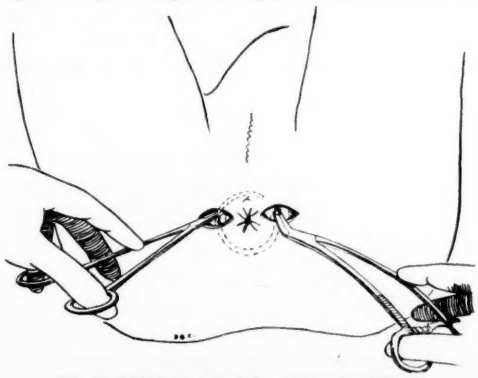

Fig. 3—Stilette passing through perineal body.

Postoperative Management

Systemic penicillin and streptomycin for five days have been given in all patients so far. The clips are removed on the fifth day. The aim must be to achieve an early spontaneous bowel action. The drugs of choice are ' Normacol ' or ' I-so-gel ' combined with ' Mil-Par '. Suppositories should be given on the third day if there has been no bowel action. Fæcal impaction must be prevented. The patient will probably have to continue taking normacol daily for an indefinite period.

Results

Seven patients have been operated on. In the first patient, the ring was too small, and while it was being inserted the anal canal was perforated. The site of operation later became infected, and the ring had to be removed. In the other six cases the operation was successfully performed with no untoward postoperative features. Fig. 4 shows the position of the ring in four different patients.

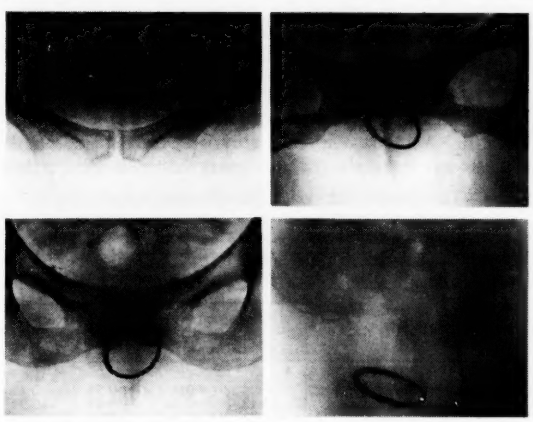

Fig. 4—Postoperative radiographs of four patients showing position of ring.

Advantages

The advantages of the operation are:

1. The operation is done with the anus closed, in a sterile field.

2. The device is, of course, of predetermined size. In the Thiersch operation the wire ligature was drawn tight, with the index finger or a no. 20 Hegar's dilator in the anal canal.

3. There is no knot.

4. The device is made of non-toxic stainless steel, is unlikely to fracture, and may be expected to remain in the tissues indefinitely (Capener 1960).

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REFERENCES

Capener, N. (1960) *Brit. med. J.* ii, 663.
Gabriel, W. B. (1948) *Proc. R. Soc. Med.* **41**, 467.
— (1953) *Amer. J. Surg.* **86**, 583.
Lenormant, E. (1903) Le prolapsus du rectum. Paris.

Preliminary Communication

HARDNESS OF LOCAL WATER-SUPPLIES AND MORTALITY FROM CARDIOVASCULAR DISEASE

in the County Boroughs of England and Wales

Schroeder,[1 2] following Japanese work,[3] found substantial and highly significant correlations between average hardness of the finished (drinking) water and mortality from cardiovascular disease in the states and large municipalities of the United States. These associations were negative—i.e., the softer the water the higher the cardiovascular death-rate. A reconnaissance using available official statistics has therefore been made in the county boroughs of England and Wales to see whether there is a case for investigation in this country. A third of the population lives in these towns, and differences in cardiovascular mortality among them are well recognised. Around the 1951 census, for example, in men aged 45–64 there was a range of 168–382 per 100,000 in coronary heart-disease and of 82–182 in cerebrovascular disease.[4]

DEATH-RATES AND HARDNESS OF WATER

Correlations were calculated between (*a*) *death-rates* from thirty-eight causes and groups of causes of death in 170 sex-age brackets (i.e., in every instance where data were available and numbers at all adequate), and (*b*) *indices of average hardness* of the local water as finished and delivered into supply in the 83 county boroughs. The correlation coefficient is a useful method of exploring a question such as this. The distributions being examined, however, are sometimes very skewed, and problems therefore arise which we are trying to solve in various ways.

TABLE I—ASSOCIATIONS BETWEEN HARDNESS OF FINISHED WATER (1951) AND SEVERAL LOCAL DEATH-RATES (1948–54) IN THE 83 COUNTY BOROUGHS OF ENGLAND AND WALES [4–7]

Certified cause of death	Correlation (*r*) with total water hardness (p.p.m.)			
	45–64 years		65–74 years	
	M	F	M	F
I				
*Cardiovascular disease**: ..	−0·54	−0·48	−0·54	−0·43
Cerebrovascular disease ..	−0·42	−0·44	−0·41	−0·33
Coronary heart-disease ..	−0·39	−0·28	−0·18	−0·09
"Myocardial degeneration", &c.†	−0·47	−0·49	−0·39	−0·45
Hypertensive heart-disease†	−0·22	−0·07	−0·23	−0·17
Remainder—hypertension without mention of heart-disease, diseases of arteries, veins, &c.†	−0·07	−0·05	−0·27	−0·18
II				
Other disease:	−0·19	−0·28	−0·24	−0·25
Respiratory disease.. ..	−0·18	−0·18	−0·22	−0·19
Bronchitis	−0·26	−0·23	−0·30	−0·27
Pneumonia	−0·06	−0·11	−0·01	+0·06
Tuberculosis	−0·06	−0·05	−0·05	−0·14
Cancer, all	−0·12	−0·24	−0·12	−0·22
Lung, &c.	−0·03	−0·08	+0·02	+0·09
Stomach	−0·19	−0·17	−0·17	−0·26
Breast	—	+0·07	—	+0·12
Remainder	−0·07	−0·27	−0·07	−0·22
Peptic ulcer	+0·11	—	+0·25	—
Accidents‡	−0·11	−0·11	+0·13§	+0·06§
Diabetes†	+0·08¶	−0·10¶	—	—
Chronic nephritis, &c.† ..	−0·00	−0·30	−0·31	−0·18
All causes	−0·39	−0·40	−0·50	−0·40

* International statistical classification, nos. 330–334, 410–468.
† 1950–58. ‡ 1950–53. § 65+.
¶ All ages, but overwhelmingly over 45.

For normally distributed variables, these are the significance levels of the product moment correlation coefficient (*r*) for 83 pairs of observations:

r >	*P* <
0·22	0·05
0·28	0·01
0·36	0·001
0·42	0·0001

Table I gives the results for the leading causes of death, and some others of special interest, in middle age and at 65–74. Attention may be drawn to several features. There are striking correlations (part I, line 1), all negative, between water hardness and total cardiovascular mortality: the softer on average the local water in the county boroughs of England and Wales, the higher on average the cardiovascular death-rate. Among the groupings within cardiovascular disease (there is no choice about these) the correlations are substantial and highly significant for deaths from vascular lesions of the nervous system and for those certified to "myocardial degeneration", &c. In coronary heart-disease the correlation is sizeable only in middle-aged men. Correlations with mortality certified to hypertension and other cardiovascular causes are not remarkable.

Correlations with non-cardiovascular causes of death (part II of table I) are small and mostly insignificant at the 1% level. The main exception is bronchitis, and this is interesting in view of the several connections between bronchitis and heart-disease. The correlations for non-cardiovascular mortality ("other disease") when bronchitis is excluded fall to −0·12, −0·26, −0·13, and −0·20.

Correlations in diabetes are negligible, and with chronic nephritis, &c., irregular. (There are too few deaths to attempt any study of stone.)* There are no other results of interest.

LOCAL WATER-SUPPLIES AND OTHER LOCAL FACTORS

The main problem in this kind of "ecological" study is to determine whether the correlations found between water hardness and cardiovascular disease are likely to represent cause and effect, or whether they merely reflect other factors with which both the water and the mortality are associated. Thus, so far as the county boroughs are concerned, soft water is found mainly in Lancashire, the West Riding of Yorkshire, and South Wales. There may be host factors in the population which are responsible for the high mortality from cardiovascular disease in these regions, and water softness could be fortuitous: alternatively other environmental factors in these regions may be responsible. For example, the softness of local water was one of the reasons why the industrial revolution (cotton, wool) started in south-east Lancashire and the West Riding: it may be that industrial and urban conditions increase the cardiovascular death-rate, again regardless of the composition of local water.

Much more work will have to be done on these questions. Meanwhile, it is worth noting that although mortality in general is high in the three main soft-water areas, it is only in cardiovascular disease that important correlations between mortality and the water-supply

1. Schroeder, H. A. *J. Amer. med. Ass.* 1960, **172,** 1902.
2. Schroeder, H. A. *J. chron. Dis.* 1960, **12,** 586.
3. Kobayashi, J. *Ber. Ohara Inst.* 1957, **11,** 12.
4. Social Medicine Research Unit and Registrar-General, Quarterly Return no. 432, appendix D, 21, 1956. H.M. Stationery Office.
5. Registrar General, Statistical Review of England and Wales, 1948–58; part I (tables, medical). H.M. Stationery Office.
6. Registrar General, Decennial Supplement, England and Wales, 1951; area mortality, 1950–53. H.M. Stationery Office.
7. Registrar General, Census, 1951, England and Wales; population tables. H.M. Stationery Office; and unpublished data.

* Causes of death and groups of causes have been analysed as presented in the tables of the Registrar General. Those of deaths certified to diabetes and hypertension are difficult to interpret. In the case of bronchitis it is worth remembering that there is considerable interchange of this diagnosis with "myocardial degeneration" on death certificates. A more general problem is the doubtful validity of specific certified causes of death after 65 or 70 years of age. (See ref. 9 opposite.)

appear—i.e., there seems to be a specific relationhip between water and cardiovascular mortality. Furthermore, when the county boroughs of Lancashire, the West Riding, and South Wales are excluded from the calculation, substantial and highly significant correlations between water hardness and cardiovascular death-rates are still found among the remaining 51 towns—a good test in itself of the hypothesis.

Comparison *within regions* is helpful in this kind of problem. When this is done, the results in general agree with the national figures. However, Birmingham, with very soft water, has low mortality similar to the neighbouring Midland county boroughs with their hard water. This observation may well be crucial, though difficult to interpret in view of the traffic and exchange there is among people, food, and drink across local boundaries within a region.

TABLE II—ASSOCIATIONS BETWEEN HARDNESS OF FINISHED WATER (1951) AND LOCAL SOCIAL INDICES IN THE 83 COUNTY BOROUGHS

Social index*	Correlation (*r*) with total water hardness
Social-class composition[13]	−0·08
Education (proportion leaving school before 15 years)[13]	−0·15
Population density[13]	−0·06
Domestic overcrowding[13]	+0·04
Air pollution—domestic[13]	−0·17
,, —industrial[13]	−0·22
Industrial rating[10]	−0·14
Cigarette smoking†	−0·20
Wages[14]	+0·11
Managers (%)[8]	+0·09
Unemployment (1951)[8]	+0·15
,, (1927–38)[15]	−0·10
General practitioner services[11]	−0·02
Prescription frequency[11]	−0·25
Fertility-rate (1927–38[15]	+0·13
Infant mortality (m.)[9]	−0·18
Mortality 1–4 years (m.)[9]	+0·11
Road-accident mortality, all ages (m.)[9]	−0·07

*Indices are for a period within 1948–54 unless otherwise stated. Significance levels as in table I.
†Information from trade sources.

In brief, questions must be asked whether the association with water is a matter of regional variation. Equally, it must be asked, might regional differences in cardiovascular mortality be due in some measure to differences in their water-supply? Intensive study of this will mean extending the analysis beyond the county boroughs—a daunting prospect. The same problems are arising in the United States.[12] It seems unlikely that the same regional factors associated with cardiovascular mortality could be producing indirect correlations with water-supply both in the United States and in England and Wales, and as remarkable if different regional factors happened to do so. In England mortality in general, cardiovascular and other, is higher in the North, but this latitude factor has been found to be irrelevant to the main problem. Correlations between water hardness and local rainfall, temperature, and sunshine averages in the county boroughs will shortly be available.

SOCIAL ENVIRONMENT

Some progress has been made with the problem of possible confounding social factors. Correlations were calculated between water hardness in the county boroughs and a wide variety of local environmental indices (table II). Only two of these correlated significantly at the 5% level with water hardness, and none did so at 1%. The associations with air pollution may be relevant; but, when correlations were recalculated to eliminate the effects of air pollution, those between cardiovascular mortality and water hardness were scarcely affected, while the highish correlations already mentioned between bronchitis and water hardness dropped sharply.

So far, then, there is no indication that local water hardness is merely indicating some important social-environmental cause of death from cardiovascular disease. Some interesting associations were, of course, found between some of these social indices and local death-rates, and these will be described elsewhere.

TABLE III—ASSOCIATIONS BETWEEN HARDNESS OF FINISHED WATER (1958) AND DEATH-RATE FROM CARDIOVASCULAR DISEASE (1948–54) IN 53 COUNTY BOROUGHS

Water	Correlation (*r*) with mortality from cardiovascular disease			
	45–64 years		65–74 years	
	M	F	M	F
Total hardness	−0·55	−0·44	−0·53	−0·36
Temporary hardness (carbonate)	−0·52	−0·50	−0·54	−0·40
Permanent hardness (non-carbonate)	−0·42	−0·18	−0·33	−0·14
Calcium (as Ca)*	−0·65	−0·58	−0·60	−0·45
Magnesium (as Mg)	−0·04	+0·08	−0·09	+0·05
Sulphate (as SO_4)†	−0·24	−0·04	−0·14	+0·01

For normally distributed variables the significance levels of the correlation coefficient (*r*) for 53 pairs of observations are:
$r > 0{\cdot}27$, $P < 0{\cdot}05$; $r > 0{\cdot}35$, $P < 0{\cdot}01$; $r > 0{\cdot}44$, $P < 0{\cdot}001$.
There is little change in total water hardness in the county boroughs comparing 1931, 1951, and 1958.
*Correlations with coronary heart-disease are −0·52, −0·41, −0·31, and −0·28; with cerebrovascular disease −0·48, −0·43, −0·52, and −0·35.
†48 county boroughs.

CONSTITUENTS OF THE WATER

Work is proceeding on this. Table III gives the results for the 53 county boroughs with the fullest data. These are mainly larger towns, and they seem to be representative (line 1 of table III corresponds to line 1 of table I). Table III probably gives the best information on local water in the present communication. Correlations with cardiovascular mortality are high for calcium content, contrasting remarkably with magnesium. These are the

TABLE IV—HARDNESS OF FINISHED WATER (1958) AND DEATH-RATE FROM CARDIOVASCULAR DISEASE (1948–54) IN THE COUNTY BOROUGHS OF ENGLAND AND WALES FOR MALES AGED 45–64

Water hardness (p.p.m.)	No. of county boroughs	Death-rate per 100,000
Total hardness*:		
< 50	25	664
50— 99	13	658
100—149	9	601
150—199	10	550
200—249	10	557
250+	16	543
Temporary hardness*:		
< 15	17	681
15— 49	19	626
50— 99	12	624
100—149	12	564
150—199	10	554
200+	13	542
Calcium (as Ca)†:		
<10	7	660
10—24	13	654
25—49	6	629
50—74	12	562
75—99	10	558
100+	5	506

*83 county boroughs. †53 county boroughs.

8. Registrar General, Census, 1951, England and Wales; occupation tables. H.M. Stationery Office.
9. Morris, J. N. Uses of Epidemiology; Edinburgh, 1957.
10. Ministry of Housing and Local Government, 1951; rates and rateable values in England and Wales. H.M. Stationery Office.
11. Ministry of Health, Annual Report, 1955, part I; the National Health Service, appendix XVIII, table G. H.M. Stationery Office; and unpublished data.
12. United States Public Health Service, personal communications, 1961.
13. Daly, C. *Brit. J. prev. soc. Med.* 1959, **13**, 14.
14. Wilkins, L. T. *Appl. Statist.* 1952, **1**, 27.
15. Morris, J. N., Titmuss, R. M. *Med. Offr*, 1944, **72**, 69, 77, 85; and unpublished data.

main cations present in British drinking water; no figures for others (e.g., sodium) are available.†

RANGE OF MORTALITY

Table IV illustrates the kind of variation of mortality with water hardness that has been found.

FURTHER WORK

Clearly there is a case for further inquiry, and several lines have already been suggested. It will be possible to extend the mortality analysis to social class, if not to occupation. Historical study of local death-rates from cardiovascular disease is proving very laborious. There is no suggestion that increase in water softening in recent years may be importantly involved in the recent increase of coronary heart-disease (in any event the coronary correlations are less impressive than those with cerebrovascular disease, and there is no suggestion of any rise in the incidence of the latter). Postmortem material may give a clue to which of the main elements of cardiovascular disease in middle age—mural atheroma, intravascular thrombosis, hypertension [16]—is specially involved. It must be emphasised that all data presented refer to mortality, and some attempt will have to be made to study incidence and morbidity. Ad-hoc examination of samples of *drinking* water will need to be undertaken. Several modes of action of water vis-a-vis cardiovascular disease suggest themselves: hard water may be protective because of its mineral content (cf., fluorine and dental caries) or, conceivably, soft water could carry harmful trace elements into supply. Both of these, and other possibilities, will have to be investigated.

CONCLUSION

The softer the water-supply in the county boroughs of England and Wales the higher the local death-rate from cardiovascular disease tends to be. What this means is not at present clear, and further investigation is indicated.

We are greatly obliged to the water authorities of the county boroughs and their chief officers, and to Dr. E. Windle Taylor of the Metropolitan Water Board, for their generous cooperation. We are also most grateful for access to I.B.M. computers, including many services by the I.B.M. Applied Science Division and its representatives. The General Register Office, the Ministries of Health and of Housing and Local Government, Prof. C. J. O. R. Morris and Prof. F. L. Warren of the London Hospital Medical College, and the computing and clerical staff of the unit have given us much help.

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†It is interesting that the *non*-cardiovascular mortality and the calcium content of local water also show correlations, but these are largely due to an association of calcium with latitude. The correlations between calcium and cardiovascular mortality are little affected by the latitude factor; they remain substantial and highly significant when latitude is eliminated by partial correlation.

16. Morris, J. N., Crawford, M. D. *Lancet*, 1961, i, 47.

Additional References:
Ministry of Health, Report on Water Softening, England and Wales, 1949. H.M. Stationery Office.
Hollingsworth, D. F. *Chem. & Ind. (Rev.)* 1956, p. 1510.

New Inventions

AN ELECTRONIC URINE ALARM

THIS instrument is used in conjunction with a metabolic cot,[1] to give an audible or visible warning when urine is passed, so facilitating prompt collection without loss.

A funnel (fig. 1), fitted with a pair of small lead-coated electrodes, is placed in the cot over a collection beaker. Connections from the funnel lead to the control unit (fig. 2), which is on a shelf under the cot. The electrodes form part of the base circuit of a transistor, which drives a miniature Carpenter relay. When there is no urine between the electrodes, the transistor is " cut off " and the relay lies in position A. With urine present, the transistor conducts and the relay takes up position B. In this position power is supplied to the alarm circuit, and the lamp will light, or the buzzer sound, for a period determined by the time constant R–C. After this period, the relay returns to position A, and the cycle repeats itself as long as urine remains in the space between the electrodes. On the alarm being given, a nurse removes the rubber stopper from the funnel, and the urine drains into the beaker, in which it can be weighed.

1. Farquhar, J. W. *Lancet*, 1960, ii, 1152.

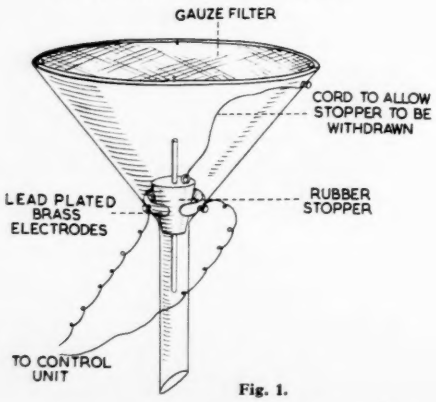

Fig. 1.

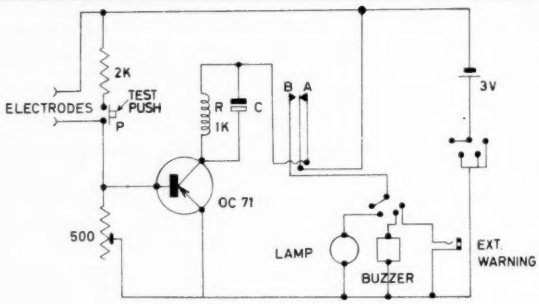

Fig. 2.

The unit is also suitable as an enuresis alarm with electrodes in contact with the body. Unlike simple circuits consisting of a bell or buzzer and battery in series with the electrodes, no induced voltage is present.

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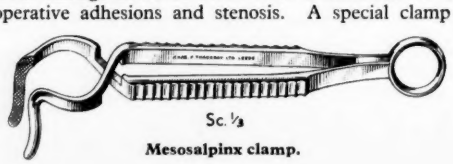
A MESOSALPINX CLAMP

THE delicate operation of salpingostomy is simplified if the mobility of the fallopian tube is controlled. Hæmorrhage and peritubal damage must be reduced to a minimum to avoid postoperative adhesions and stenosis. A special clamp has



Mesosalpinx clamp.

been designed which allows full control of the area of operation and secures a blood-free field (see figure). The instrument is so shaped that the curved blades can be applied to the mesosalpinx between the ovary and the tube. The fallopian tube is protected by a ring which is at right angles and proximal to the blades which are applied to the tube. A second clamp can be placed on the mesosalpinx medial to the ovary. The clamp blades can be sheathed with thin rubber-tubing if necessary. Tension on the blades is controlled by a spring, and the surgical assistant is able to manipulate the operative site from the ring handle without crowding the restricted area of operation.

I am indebted to Messrs. Chas. F. Thackray, Park Street, Leeds, 1, from whom it may be obtained, for the manufacture of the instrument.

Oldham Hospitals Group, Lancashire. P. C. STEPTOE F.R.C.S.E., M.R.C.O.G.

Reviews of Books

Human Factors in Jet and Space Travel

Editors: S. B. SELLS, PH.D., professor of psychology, Texas Christian University; CHARLES A. BERRY, M.D., lieutenant-colonel, U.S.A.F., chief, flight medicine branch, aerospace medicine division, Office of the Surgeon General. New York: Ronald Press. 1961. Pp. 386. $12.

DESCRIBED by the publishers as "a medical-psychological analysis", this book is indeed edited by a medico-psychological partnership. The psychological problems of jet flying and space travel receive a generous allowance of the text, but one that is justified and not out of proportion to the importance of the subject.

There are fourteen expert contributors, and it is not easy to induce fourteen pens to conform to the same literary standards; but the best of the writing is very good indeed. Apart from an occasional sentence, usually a quotation, the turgid juxtapositions of esoteric words and phrases which can make scientific books and papers so tiresome are sternly excluded, and the book is easy to read.

The content is admirable. To a subject which lends itself to exaggeration, the authors apply the disciplines of simplicity, reason, clarity, and objectiveness. The range of the book is considerable, from the public-health aspects of jet travel to man's needs in Space; from the transport of invalids by air to the selection and training of astronauts; from temperature control in passenger cabins to cosmic radiation; from noise to microwave radar. There are, naturally, statements with which not all would agree: the half lethal dose of acute whole-body radiation, for example, is put at 700 r. There are some omissions, such as a reticence on the value of backward-facing seats in passenger aircraft, and one or two misprints (the surface-area of the body is given as 2 $cm.^2$). But, on the whole, the book admirably achieves its object—to be "a comprehensive sourcebook on human-factor aspects of jet and space travel", and, a few mathematical paragraphs apart, is easily read and comprehended by the doctor with no special knowledge of aviation medicine. It is equally valuable to those with professional interests in aviation, since it contains, in one well-printed volume, much previously scattered information. A complete list of references follows every chapter, and there is a comprehensive index in two parts, one by names and one by subjects.

A Laboratory Handbook of Blood Transfusion Techniques

A. DEREK FARR, F.I.M.L.T., senior technician, National Blood Transfusion Service, Wales Region. London: Heinemann Medical Books. 1961. Pp. 135. 17*s*. 6*d*.

THIS small book deals with the details of blood-transfusion work that are often only outlined in books on blood-group serology. Blood-grouping has, of course, a place in the book, but only in so far as checking the group of bank blood and cross-matching with recipient's blood are concerned. The bulk of the text is devoted to very comprehensive descriptions of the methods for preparing and administering stored blood, for preparing apparatus and solutions, and for preparing plasma and serum for administration. The object is to cover the syllabus of the Institute of Medical Laboratory Technology certificate in hæmatology and blood-transfusion, and there is no doubt that candidates for this certificate will here find everything they want to know. There is, for example, a proper description of the nature of pyrogens and of the methods of testing for them; another good and not overcomplicated section deals with transfusion reactions. For the most part use of the standard National Blood Transfusion Service apparatus is assumed, but newer apparatus including disposable plastic apparatus is adequately described. The book can be recommended as a useful supplement to the accounts of blood-grouping techniques.

Radiation Injury in Man

Its Chemical and Biological Basis, Pathogenesis and Therapy. EUGENE P. CRONKITE, M.D., head, division of experimental pathology, Medical Research Center, Brookhaven National Laboratory, Upton, New York; VICTOR P. BOND, M.D., PH.D., head, division of microbiology, Medical Research Center, Brookhaven National Laboratory, Upton, New York. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960. Pp. 298. 52*s*.

THIS book gives an excellent and readable survey of the radiobiological basis of radiation injury in man. The first eight chapters cover the physical aspects and biological effects of ionising radiation, and the last four deal with clinical effects in man including diagnosis and therapy of the acute effects and an account of long-term and low-level radiation effects. The authors urge the doctor to take greater responsibility for control of hazards from radiation.

The physician and medical student will find the glossary of radiation terms helpful; but there is no corresponding glossary of medical terms for the non-medical reader, though the book is also intended for science teachers and technicians. The sections dealing with acute radiation disease in man are particularly good, and it is clear that the authors have been concerned with the treatment and investigation of radiation injuries due to nuclear accidents in the United States.

The fallout from nuclear explosions has raised the background level of radiation throughout the world, but there is as yet no direct evidence of what effect this will have on man. Many of the arguments about it are based on radiation effects in mice or fruit-flies subjected to relatively large doses. In the last chapter, dealing with the effects of exposure to fallout, the authors give an impartial view of the evidence, and sensibly conclude that until sufficient data are available the only rational course is to reduce the level of radiation exposure of the general population to the absolute minimum consistent with good medical practice and progress in the use of atomic energy.

Belfast and its Charitable Society

A Story of Urban Social Development. R. W. M. STRAIN. London: Oxford University Press. 1961. Pp. 333. 45*s*.

THE opening minute of the Belfast Charitable Society bears that at a meeting of gentlemen held at The George on Aug. 28, 1752, "to consider of a proper way to raise a sum for building a Poor house and Hospital . . . in or near the Town of Belfast", it was resolved to issue 100,000 tickets at half a guinea each, "the chances whereof to depend upon the drawing of the Dublin lottery now depending". The lottery project miscarried, but the Charitable Society was born very much alive, and for many years played a major part in the care of the less fortunate among the townspeople, and indeed in the life of the town itself; for not only did it care for the deserving poor (sparingly, after the fashion of the times) but it also provided a wide range of social services—house of correction, hospital, burial ground, even water-supply: for some 45 years the society was entirely responsible for the water-supply of Belfast. By 1775 medical provision under its auspices included accommodation in the Infirmary, admittedly simple, for medical and surgical cases as well as visitation of the sick in their own

homes. In 1777 a nurse keeper was appointed to look after the Infirmary patients: she was to have " her diet and 18*d.* weekly " and a boarded enclosure was to be provided for her bed " in the Right Angle of the large ward, at entrance—eight feet square ".

In those days " enoculation " of the children in the poorhouse was practised against smallpox, and in 1800, following Jenner's discovery, it was resolved " that inoculation for the Cowpox " be tried on a few of the children, provided their parents freely consented, the directors having been assured " that it is not infectious—that it is an easier disorder than the smallpox and that those who have had it are not liable afterwards to receive the infection of the smallpox—as certified by a number of the most respectable physicians in England ".

The care of children inevitably formed a large part of the work of the society: when they were considered ready to be apprenticed an advertisement was inserted in the local newspaper and it was estimated that there might be nearly 300 poorhouse children under apprenticeship at any one time. The average age on being apprenticed was 11 or 12 years, but children were occasionally bound as early as 8 or 9. The society seems to have been reasonably careful in its choice of masters and tried to maintain some degree of supervision even if the child went some distance from Belfast; apprentices were visited at least twice a year, but cases of cruelty did occur. In time, the levy of a poor-rate seriously affected the finances of the society, the public taking the view that once the Government was providing for the very needy through the guardians there was no longer any need for voluntary effort. Similarly, the gradual evolution of administrative machinery steadily whittled away others of the functions the society had assumed, and Dr. Strain's work, obviously a labour of love, provides an interesting study of urban social development.

Fundamentals of Nerve Blocking

VINCENT J. COLLINS, M.S., M.D., associate professor of anesthesiology, New York Medical Center, and anesthesiologist, Bellevue Hospital Center. London: Henry Kimpton. 1960. Pp. 344. 71*s.* 6*d.*

Dr. Collins, assisted by his director, the late Professor E. A. Rovenstine, has conveniently divided his subject into two parts. The first is concerned with the principles and uses of nerve blocks, which are ably discussed, especially in relation to diagnostic and therapeutic procedures. Many British clinicians will not share the author's views about the value of nerve blocks in the assessment of vascular disease. The place for this form of treatment in the control of various forms of pain is, however, convincingly debated. In the second part Dr. Collins describes concisely, and with the aid of clear and simple diagrams, techniques for all the different nerve blocks.

This book is a résumé of teaching and practice at the Bellevue Hospital, where the first pain clinic was formed. Any anæsthetist starting his own pain clinic will find it invaluable, and others will find it very helpful in broadening their knowledge of regional anæsthesia.

An Approach to Old Age and Its Problems

MARGARET NEVILLE HILL, C.B.E. Edinburgh: Oliver & Boyd. 1961. Pp. 133. 15*s.*

THE distinguished author of this book has been a pioneer in the creation of old people's homes of many kinds. Her mother was a member of the Cambridge board of guardians at the beginning of the century. Mrs. Hill describes the Cambridge workhouse as it was then, and she has been concerned with the needs of the aged ever since.

The first half of the book is a history of the development of services for the care of the elderly, particularly those Mrs. Hill has herself pioneered. The second half, much more engaging reading, discusses the problems that arise in old people's homes. She insists that homes should be of more than one kind. Homes of the hotel type should provide for those people who are just too frail to maintain complete independence, and who can thereby be saved from loneliness and decay. There is a place too for homes with communal dormitories, like the better class of welfare hostel being built by the local authorities today. There is a need too for old people's convalescent homes and halfway houses to bridge the gap between hospital treatment and return home. And there is a special place for homes for the permanently infirm who need a little more nursing than an ordinary home can offer but do not need to remain permanently in hospital. Mrs. Hill also urges the provision of hostels for the mentally infirm, who can cause disruption in any community geared to the needs of the mentally normal.

This book is a highly personal account, but it is full of the wisdom of long experience. Its greatest value will be to social workers and to those trying to provide or run old people's homes.

Progress in Endocrinology (*Memoirs of the Society for Endocrinology, no. 9 and 10.* London: Cambridge University Press. 1961. Part I: Pp. 166. 45*s.* Part II: Pp. 167. 45*s.*).—These two volumes, edited by Dr. K. Fotherby, Dr. J. A. Loraine, Dr. J. A. Strong, and Dr. Peter Eckstein, are a record of the meeting held jointly by the Society for Endocrinology and the Endocrine Societies representing the *Acta-Endocrinologica* congresses, in Edinburgh in August, 1959. Part I reports recent work on neuro-endocrinology and on the endocrinology of the thyroid and parathyroid glands. Part II contains a review by Prof. G. F. Marrian of recent research in the biochemistry of œstrogens, a symposium on the relation of the endocrine glands to cancer, and short papers dealing with the biochemistry and biological action of steroid and protein hormones.

Discussions on Child Development (*Vol. 4*: Proceedings of the Fourth Meeting of the W.H.O. Study Group on the Psychobiological Development of the Child, Geneva, 1956. London: Tavistock Publications. 1960. Pp. 186. 30*s.*).—In this, the crowning and most important volume of a remarkable series, Piaget attempts first to draw the previous discussions together and poses questions to his colleagues from other disciplines—in particular to Lorenz, Bowlby, Margaret Mead, Grey Walter, and Tanner. To the dimensions of inheritance and physical and social environment, he adds a fourth factor—equilibration—explicable in cybernetic terms. These papers form half of the book (edited by Dr. J. M. Tanner and Prof. Bärbel Inhelder), the latter part of which is the usual verbatim report of the final discussions between 16 experts. Many readers will find the volume heavy going, but a debate on the nature of human growth and life between such minds as these could hardly be otherwise—a unique occasion indeed, and a volume to study and treasure.

Textbook of Medicine (13th ed. Edinburgh: E. & S. Livingstone. 1961. Pp. 989. 45*s.*).—This famous textbook has now passed its thirtieth birthday under the guidance of its originator, Sir John Conybeare, who has lately had the aid of Dr. W. N. Mann. Its vitality endures and it shows few signs of ageing. This edition is notably strengthened by a new section on renal disease by Prof. M. L. Rosenheim; and it is a remarkable achievement to have included an article on the workings of the Mental Health Act, which came into operation less than six months ago. The book, as always, is beautifully written. Only the sections on blood diseases and alimentary diseases seem in need of a little renovation. It is surprising, for example, to find no mention of bone-marrow examination in the diagnosis of pernicious anæmia. The benzidine test for occult blood is advocated, although benzidine went off the market three years ago; and the now discredited fractional test-meal is still recommended. There has long been an excellent chapter on the diseases of small children: perhaps the next edition may have a section on the medicine of old age. The book, pleasant to handle and still modestly priced, will certainly keep its place among the best English textbooks of medicine.

Medical Directory 1961 (London: J. & A. Churchill. In two parts. £5).—The 117th issue of the directory is now available. This year it contains 95,740 names, almost 2000 more than in 1960.

THE LANCET

LONDON 22 APRIL 1961

Science, Government, and Democracy

Sir CHARLES SNOW has a valuable talent for provoking controversy: he did it with his Rede lecture, and he has done it again with his Godkin lectures to Harvard University, which have now been published under the title of *Science and Government*.[1] Here with a novelist's pen he depicts those unusual characters Sir Henry Tizard and F. A. Lindemann, later Lord Cherwell, and describes what he considers to be the effects of their dissensions on the application of science to the air defence of this country during the war. Friends of each have defended their hero in print, and there is no need here to discuss which was the more right. More important are the general principles which in SNOW's opinion, these events illustrate.

The main question which he raises is to what extent science can influence the decisions of the Government, and how this can best be achieved. He holds that bodies like the Tizard Committee, which was set up for the scientific study of air defence, are " in the right conditions as sharp a tool for doing business as government can find ". Those conditions are that " the objective must be clear and not grandiloquently vast ", the committee has to be " placed within the government structure ", and it has to possess or take powers of action. " Advisory committees, if they are confined to pure advice and never get near the point of action, fade away into a kind of accidie ". SNOW's comments on medicine in this context are brief, but to the point. " Some of the most important choices about a nation's physical health," he says, " are made, or not made, by a handful of men, in secret, and, again in legal form, by men who normally are not able to comprehend the arguments in depth." He sees a resemblance between medicine and military science in that in medicine " the objectives are often as clear-cut as in military science ", and " it is not the nature of the objective that makes for speedy action, whether it is destructive or on the side of life. All that matters is that there should be an objective at all ".

If in the sentence quoted above SNOW is referring to the fact that both the Minister of Health and his Permanent Secretary are laymen, health does not differ from any of the Service Ministries, or, indeed, any other Ministry which has to deal with technical matters; and the vast majority of day-to-day decisions on health issues never come within the purview of laymen at all, but are decided by, or on the advice of, the Minister's medical officers or ad-hoc medical committees. It is different where finance is concerned, however, and the history of the National Health Service since 1948 has shown again and again that major questions of policy vital to its development have been decided at Treasury or Cabinet level without any evidence that those taking the decision were " able to comprehend the arguments in depth ", or, if they were, that they paid sufficient heed to them.

But there is even more formidable evidence of a failure to make the right choices for lack of the right scientific advisory machinery. The present graded system of hospital staffing was organised between 1946 and 1948 and was admittedly based on the structure existing in 1939: it has since been treated as sacrosanct. Considering the accelerating acceleration of medicine during the past twenty years it is not surprising that many people, especially among the younger consultants and the registrars, regard it as in some important respects already out of date. Yet the Platt Committee set up to consider current problems of hospital staffing did not really deal with this fundamental question. Fifteen years ago it may have been reasonable to view whole-time posts with suspicion, but is it rational today; and should there not be an impartial inquiry into their place in hospital staffing? And may there not be a place, too, for the " geographical whole-time " post acceptable in the United States, which allows a consultant to combine paid hospital work, private practice, and research, provided they are all done at the hospital? At present no such appointment is possible in the health service, nor does the University of London allow it, though there is much to be said for such a combination of health-service and academic posts, especially the opportunities for research which they offer to the part-time consultant. At present the health service positively discourages research by making it financially more advantageous for the young consultant to obtain maximum part-time sessions than to continue with any research he may previously have been doing.

SNOW pays a well-deserved tribute to the Medical Research Council " working with funds Americans would think derisory ": actually the Government spends on the Medical Research Council the cost of a packet of ten cigarettes per head of the population per annum.

Whose function should it be to find answers to these and many other equally important questions relating to the health service? If SNOW is right about the conditions necessary for the success of such an attempt, the appropriate committees should be an integral part of the structure of the service and should possess " powers of action ". There seems to be the rub. For years now proposals for a permanent grade below that of a consultant have been put forward, debated, modified, and withdrawn. The Platt Committee's latest proposal looks as though it may run the same course. " We are becoming existential societies," writes SNOW, " and we are living in the same world with future-directed societies. . . . We seem to be flexible, but we haven't any model of the future before us. In the significant sense we can't change. And to change is what we have to do." Democratic parliamentary procedure does at least provide for decisions, but the method of democratic procedure employed within the health service, whereby decisions await indefinitely the outcome of discussions with interested corporations, may lead to no decision being reached at all. Democracy has its own laws of

1. London: Oxford University Press. 1961. Pp. 88. 9s. 6d.

thermodynamics, which are that the heat generated by a new proposal is proportional to the number of particles involved; the time taken for discussion is proportional to both; and inactivity is a function of all three. Is the epitaph of democracy to be " the debate continues " ?

Antibiotic Policy and the Staphylococcus

To be restricted or not to be restricted, that is the question. In the early days of antibiotics their use was limited only by the difficulties of manufacturing them on a large scale, and, as supplies became adequate, restriction seemed absurd. It was clear to everyone in the 1940s that penicillin had rung the death-knell of the streptococcus and that streptomycin was about to do the same for the tubercle bacillus. Gradually the versatile staphylococcus taught us the dangers of widespread and indiscriminate antibiotic therapy, and when in 1952 erythromycin appeared on the scene there was very wide agreement that this antibiotic, at least, should be used with discretion. In the ensuing years an increasing number of investigators recommended a more general restriction in the use of antibiotics, and the staff of some hospitals even adopted a policy for the control of all antibacterial drugs used in the hospital.

This viewpoint is emphasised in a recent paper by WALLMARK and FINLAND.[1] A total of 1550 strains of coagulase-positive staphylococci from patients in the Boston City Hospital in five different years between 1950 and 1960 were examined for antibiotic sensitivity and phage-type. As has been noted in many other hospitals the incidence of staphylococci of phage-group I increased during the ten years, and this was largely due to an increase in the prevalence of strains of type 80/81. Strains of group III showed a corresponding decrease, and there were changes in the occurrence of types within the group. In spite of these changes in the prevalence of certain phage-types the proportion of strains resistant to the widely used antibiotics continued to increase. A clear correlation was noted between the isolation of antibiotic-resistant strains and the antibiotic treatment of the patient from whom they were isolated. Thus a considerably greater incidence of strains resistant to each of the antibiotics tested was obtained from patients who had received antibiotics, as compared with those from patients who had had no recent chemotherapy, although the resistance of individual strains was not specifically related to the antibiotic(s) which the patient had received. Only rarely did an originally sensitive strain show a progressive increase in resistance after exposure to a particular antibiotic. WALLMARK and FINLAND conclude that the increased incidence of drug-resistant staphylococci in the hospital was probably the result of the elimination of sensitive strains by antibiotic therapy, permitting resistant ones to multiply and spread. They call for " the exercise of great care, wise judgment and circumspection in the application of these highly useful and important agents ".

The warning is timely, for the advent of methicillin may have induced some overconfidence; and serious doubts have been expressed about the wisdom of using the new antibiotic as a ward spray.[2 3] It is, of course, well known that the only *fully virulent* staphylococci which are resistant to benzyl penicillin are the penicillinase-producing organisms isolated from clinical infections, and that the penicillin-tolerant staphylococci isolated in vitro are of too low virulence and too unstable in their resistance to penicillin to be a clinical menace. Does this mean that, since methicillin is resistant to penicillinase, staphylococci resistant to it will be of no clinical significance ?

Many investigators have shown that strains of *Staphylococcus aureus* will develop resistance to methicillin after passage in the presence of the compound in vitro,[3–6] although much less rapidly than is the case with some strains of *Staph. albus*.[3] Naturally occurring methicillin-resistant strains of *Staph. aureus* have also been reported from three different sources, although all three strains are of similar, if not identical, phage-types.[7–9] It has now been shown that some of the strains of *Staph. aureus* which have become resistant to methicillin by passage in vitro have retained the characteristics of the parent strains, including full mouse virulence, and that the degree of resistance of these strains remains stable after repeated subculture in the absence of the antibiotic.[10] Such methicillin-resistant cultures were isolated only from penicillinase-producing strains, although there was no evidence of methicillin destruction. Methicillin-resistant cultures isolated from penicillin-sensitive strains resembled penicillin-tolerant staphylococci isolated in vitro.

It is reasonable to suppose that stable, fully mouse-virulent, and methicillin-resistant strains of *Staph. aureus* are a potential menace. That they do not arise readily in vivo has been clearly demonstrated; but staphylococci do not readily become resistant to the tetracyclines, and in early reports on chlortetracycline it was suggested that tetracycline-resistant staphylococci were unlikely to be of clinical importance.[11 12] On the other hand, anxiety about resistance should not prevent the proper use of methicillin. Its active bactericidal properties and lack of toxicity make it drug number one for all severe staphylococcal infections resistant to penicillin. In hospital practice it would be reasonable to start treatment of any staphylococcal septicæmia with methicillin, pending a report on sensitivities.

Now that the nucleus of penicillin has been isolated, it has been suggested that new " penicillins " can be produced in large numbers, thus eliminating the problem of resistance and making restriction in the use of methicillin unnecessary. There are two serious objections to this, even if " penicillins " could be manufac-

1. Wallmark, G., Finland, M. *J. Amer. med. Ass.* 1961, **175**, 886.
2. Elek, S. D., Fleming, P. C. *Lancet*, 1960, ii, 569.
3. Stewart, G. T. *Brit. med. J.* 1961, i, 863.
4. Rolinson, G. N., Stevens, S., Batchelor, F. R., Wood, J. C., Chain, E. B. *Lancet*, 1960, ii, 564.
5. Barber, M. *Brit. med. J.* 1960, ii, 939.
6. Fairbrother, R. W., Taylor, G. *Lancet*, March 4, 1961, p. 473.
7. Jevons, M. P. *Brit. med. J.* 1961, i, 124.
8. Rolinson, G. N. *ibid.* p. 125.
9. Knox, R. *ibid.* p. 126.
10. Barber, M. *J. clin. Path.* 1961 (in the press).
11. Paine, T. F., Jr., Collins, H. S., Finland, M. *J. Bact.* 1948, **56**, 489.
12. Finland, M., Collins, H. S., Paine, T. F., Jr. *J. Amer. med. Ass.* 1948, **138**, 946.

tured at the required rate and showed no cross-resistance. First, there is much evidence to suggest that, in the selection of drug-resistant staphylococci in hospital, strains of increased virulence emerge.[13] Secondly, too wide a use of antibiotics effective against gram-positive bacteria might increase the incidence of infection due to *Pseudomonas pyocyanea* and other gram-negative bacilli. With these reservations, the new synthetic penicillin, α-phenoxypropyl penicillin (PA-248), described in three articles in this issue, promises to be a welcome arrival. It can be given by mouth, and Dr. NAGLEY records good results in 5 cases of pneumonia associated with penicillin-resistant staphylococci in the sputum. From their study of serum levels Dr. WILLIAMSON and his colleagues believe that PA-248 will be more effective against resistant staphylococci than penicillin V or phenethicillin, and that it will be best in streptococcal infections. Dr. JACKSON and Dr. RAO compared the in-vitro activities of five penicillins against penicillinase-producing staphylococci, and their results support the findings of WILLIAMSON et al. Like methicillin, PA-248 remains active in the presence of staphylococcal penicillinase; but here again further experience is needed to show whether strains resistant to it will be of no clinical importance.

First in Orbit

IN an age when adjectives are used mainly in the superlative and prosaic events are reported as epics, it is not always easy to separate worth from mediocrity: but some achievements have a quality that no misuse of words can disguise.

The news from Moscow is no less remarkable because it has been expected. When the first animals were fired into Space, the experiments were clearly of great scientific importance: but, dog or monkey, animals are no more than passengers on the voyage. They may be startled by the noise, constrained by the acceleration, surprised by the weightlessness: but, having no anticipation, no imagination, and no recall, they lie obediently as they have been trained, passive indicators of biological functions. Electronic devices can note, record, and store data; they can even use the data to initiate action. But, versatile though they are, they cannot make rapid decisions on inadequate or ambiguous information; and they cannot anticipate an emergency or change their minds. If there is to be progress in dangerous endeavours, human wit and courage still have to be applied. The history of aviation is as much of men as of machines. Whenever the limits of knowledge are reached, a man has to be put into new conditions until enough data have been obtained to formulate new principles and new techniques.

The very qualities which make man the most suitable test pilot, whether inside the atmosphere or beyond, are those which must have been put to the greatest test in this first sortie. The launch of a large rocket, even seen and heard from a safe shelter, is a terrifying affair: the result of the least malfunction may be disastrous. From the time he entered the capsule, the astronaut must have had an hour or two to contemplate the various possibilities, while the final checks and adjustments were being made; and his awareness of all the scientific, technological, and political hopes focused on him must have made the waiting period very hard to bear. Though many men have shared the experience of awaiting tremendous and unprecedented events, only in war can any have faced a prospect containing so many unknowns and so little safe margin of error.

The natural reaction of the ordinary man to accounts of exploration involving great risk, hardship, and discomfort is to speculate on the motives of the explorer. There are barriers of thought, character, and language over which it is difficult to pass, whether to explain or to understand: what is reasonable to one is bizarre to another. But there is no doubt that the urge to discover, to see what none has seen, is strong in certain men, and that others are attracted by the stimulus of fear. Fear, as is well known, sharpens sensation and gives an edge to appreciation; hence it may become acceptable and even necessary for the zest it brings to life. This readiness to accept fear as a part of normal existence is not the same as recklessness when it is accompanied by determination, endurance, ability, and a sense of responsibility.

It will not be long before other men go into Space. Before next year is out the simple orbit may be regarded as a mere training flight for more ambitious voyages, the way to which is now open. The present success is significant not only because a rocket put a man into orbit but even more because the capsule came back to Earth. Three special difficulties have been overcome—re-entry into the atmosphere, descent into a planned area, and successful recovery. If men can go up into Space and return safely, the satellite staging-post becomes a practical proposition. Less adventurous scientists, technicians, and biologists can go out to prepare the next step forward, to the moon and beyond. Many design studies of such space stations are ready to be turned into prototypes, and the physiological problems are not greatly different from those which were solved in Major GAGARIN'S capsule. Yet what is suitable for a two-hour trip is not necessarily suitable for a long tour of duty. Artificial gravity can be provided by causing the station to rotate on its axis. This is likely to be more agreeable to the crew than prolonged weightlessness; but the gravity is bound to vary with the distance from the hub, and to affect one part of the body more than another, according to the orientation. Those who are especially sensitive may suffer some discomfort: motion sickness, in fact, may be a minor penalty of space travel. It may be possible to ignore the effects of cosmic radiation during short exposures in low orbit, but longer exposures are another matter. The radiation dose, general or focal, may be one factor which will set a limit to the tour of duty in a satellite.

All this is for the future. It is the first step that is always the most difficult and the most dangerous; and this step has now been taken. Meanwhile let us rejoice with Russia, not only that a man went and saw, but also that he came safely home.

13. Barber, M., Dutton, A. A. C., Beard, M. A., Elmes, P. C., Williams, R. *Brit. med. J.* 1960, i, 11.

The Census

ON Sunday the nation counts itself—for the sixteenth time since the first official population census of 1801—in the largest "do it yourself" social survey so far undertaken in this country. This ten-yearly stocktaking provides us with information needed to plan for the future.

Not only does the Census take the tally of heads by age and sex, from which are calculated both the vital statistics of birth, death, and marriage rates, and the proportion of the Exchequer grant to the 1700 local authorities, but it also provides a picture of the people of Great Britain as they have their being on Sunday night. The picture is, of course, anonymous so far as the individual is concerned; but the portrait of the nation will be a true likeness, "warts and all". A booklet from the General Register Office and the Central Office of Information [1] sets out clearly the information that will be sought this year. Because a random sample of 10% of the population are being asked some 23 questions, the other nine-tenths will escape with fewer than in any Census since 1891. This is a considerable advance, as those who plan surveys well know; for, according to some unwritten Parkinson's Law, the accuracy of answers to questionaries varies inversely with the number of questions asked. The majority, at any rate, will welcome the easing of their task.

Almost all the questions are of interest to medicine, directly or indirectly. The material provided by the Census, and by its offspring the occupational and area mortality tables, has been described as among the most important laboratory material to which the social medicine department has access. This is now more true than ever. The present Census will build up a picture of the household as it normally exists, and of its housing, with new questions on the type of building and form of tenure. Questions on bath, lavatory, and hot-water facilities are also included. Information on Commonwealth citizenship and nationality will for the first time show how much immigration is occurring, and from where; and also where people are settling. Taken into account with the housing information, this knowledge will help social workers and industry to plan for the local needs of the new populations. For the first time, too, information will be obtained on internal migration, so that the stream of movement of peoples from place to place within the country will be accurately charted by numbers and socio-economic condition. A knowledge of such movements, besides helping local planning, may add new meaning to disease statistics by occupation and area.

The country's portrait will be completed in a number of other ways as well, both by reframing earlier questions and by way of new ones. The age and sex structure of the population of institutions will be known, and this knowledge, used in relation to household structure, will provide facts on, among other things, the number and condition of elderly people living alone. A question on the number of hours worked in the day, together with one on previous employment, should yield much useful information on what "part-time" work really is and what kind of occupations people take up when they retire. What number of doctors, for instance, become salesmen or Civil Servants after saying goodbye to medicine? We shall also learn, at the other extreme of the working life, the extent to which people continue their education past the statutory school-leaving age. This information, together with that being sought on qualifications in science and technology, should help us to make the most efficient use of our national store of brain-power. All this, of course, is additional to the standard but essential information which will be gathered on the age of the population and family size. This tells us to plan for the reception, into higher education and employment, of the "bulges" of 1947 and the later 1950s, and for the proper housing and care of families. The size of families diminished by an average of 2 members between 1891 and 1951, whilst the proportion of the population over the age of 65 increased from 1 in 20 in 1911 to 1 in 10 in 1951.

Use of the War Office I.B.M. 705 computer for the Census should not only make it possible to rule out errors of enumeration but also permit storage of the mass of data on magnetic tape, so that it will remain accessible for future investigations. Though the cost of the Census will be something like £3 million (compared to £1¼ million in 1951), at approximately a shilling a head it must in the long run be accounted one of the best bargains of the day.

Finally, but not least important, the 1961 Census is part of the World Census Programme of 1955–64, in which over 200 countries are to make censuses in a standardised way. With a projected world population increase from 2500 million in 1950 to 6250 million by the end of the century,[2] accurate global vital statistics cannot be available too soon.

1. Why a Census? 1961. H.M. Stationery Office. Pp. 30. 1s.

Annotations

PSYCHOPATHS AND THE SPECIAL HOSPITALS

TANGLED in the meshwork of legislation on mental disorder that existed before the 1959 Act were the three "special" hospitals—Broadmoor, Rampton, and Moss Side. The first took offenders found insane on arraignment, the "guilty but insane", and ordinary prisoners who became certified, while the last two provided for dangerous mental defectives. Broadmoor could admit only those offenders who had been charged before a court, but the others were not thus restricted. Altogether they accommodate some 2500 patients. Before 1948 the Board of Control owned and ran them, and on the appointed day they were transferred to the Minister of Health although the Board continued to manage them.

With the sweeping legislative changes of 1959, in particular the dissolution of the Board of Control and the intention to treat medically a wider range of "psychopathic" cases, the future purpose and management of these hospitals became a matter for urgent study, and the

2. Hauser, P. M., Demographic Dimensions of World Politics. *Science*, 1960, **131**, 1641.

working party [1] set up by the Ministry of Health to examine the question have now reported.[2] In accordance with the spirit of the Act, the working party recommend that past restrictions should go, that future criteria for admission should be the same for all forms of mental disorder, and that admission should be primarily determined by treatment needs; but they found the greatest difficulty in defining the classes of case to be admitted. Very careful individual inquiry is needed into mental state and history, with particular reference to security needs and the adequacy (and willingness) of the local hospital to treat difficult patients. A patient should be admitted only if, in the light of these facts, all other possibilities have been judged unsuitable. The report points out that it is wrong in principle and administratively expensive to restrict a patient unnecessarily, and the fact of his admission may complicate re-entry into the community.

It is realised that the demands upon the special hospitals, with present restrictions lifted, will depend upon the development of psychopathic units elsewhere in the National Health Service (or penal service) and upon the use of "open-door" policies in ordinary psychiatric hospitals. The working party make it quite clear that regional boards should design their services to ensure a range of facilities, including some "secure" units. Treatment locally, they emphasise, should be the aim wherever possible, and they advise that, before transfer to a special hospital, the patient might be given trial treatment elsewhere in the N.H.S. so that his condition could be further assessed in different surroundings. From their inquiries, the working party deduce that only about 200 cases now in N.H.S. mental hospitals might qualify for transfer to a special hospital, and about 100 now under the Prison Commission. The special hospitals should treat as separate groups the psychopath of near-normal intelligence, the mentally ill, and the subnormal.

Quoting a subcommittee of the Medical Research Council on psychopathic personality, the working party agree upon the urgent need for research, which could best be carried out within a number of diagnostic and treatment centres (of at best 100 beds) and with security precautions) for psychopaths and possibly other offenders. The report's call for research facilities to be built into a new administrative structure at the start is very welcome. The differences between such centres and remand centres, now being provided for the penal services, are not made fully clear, but the working party wisely call for the closest possible liaison, preferably via jointly appointed psychiatrists. In practical terms the centres may need to be in two parts, a small truly diagnostic unit near a teaching hospital or university centre and a peripheral treatment unit as a separate part of a well-equipped psychiatric hospital. One or two should be developed at once, and further action planned in the light of experience: staffing, at all levels, would need to be generous, and increases in medical and allied staff at the special hospitals are called for.

Clearly some such courageous steps as these are essential if the provision of the 1959 Act dealing with psychopathic personality is not to be a dead letter.

1. The members were Mr. D. EMERY (chairman), Mr. P. BENNER, Dr. T. P. CUTHBERT, Dr. J. GRAHAM, Mr. T. C. GREEN, Dr. J. D. N. HILL, Mr. L. R. LORIMER, Dr. J. S. B. MACKAY, Dr. W. S. MACLAY, Dr. R. F. G. ORMROD, Dr. P. D. SCOTT, Dr. D. H. H. THOMAS, and Mr. G. G. HULME (secretary).
2. Special Hospitals. Report of Working Party. H.M. Stationery Office. Pp. 24. 1s. 3d.

FERROUS-SULPHATE POISONING IN CHILDHOOD

THE incidence of acute accidental iron poisoning in children has probably increased in the past decade, judging from the growing number of published accounts [1–4]; and ferrous sulphate now ranks second only to aspirin as the most important single childhood poison. Owing to the brightly coloured sweet-like appearance of the tablets, the ingestion of the entire contents of a container is usual, and such massive overdoses carry a mortality of 50%. In laboratory animals, doses of iron exceeding 200 mg. per kg. body-weight are always fatal, and as little as 3 g. of the sulphate (i.e., nine gr. 5 tablets) have proved fatal in a small child.[5]

Those most at risk are aged 1–2 years; and in this country a common source is the free supply of tablets to expectant mothers attending clinics. Warning labels are now affixed to all containers, but inevitably maternal ignorance and crowded home conditions perpetuate this special hazard to the youngest members of the family. Even a difficult stopper or keeping the box "out of reach" may be thwarted by an older child who retrieves the tablets and well-meaningly feeds the baby with them. In prevention, repeated warnings of the hazards seem to be of some value.[4] Some iron salts may be safer than others [6]; and the adoption of a plain preparation, such as 'Fersamal' (ferrous fumarate, Glaxo), which is not sugar-coated and is unattractive to children, has much to commend it.

The clinical picture is characterised by three phases. The first, quickly following ingestion, is attributed to the highly corrosive action of iron salts on the gastrointestinal mucosa. Vomiting, sometimes as soon as thirty minutes after ingestion, heralds a rapid sequence of pallor, shock, hæmatemesis, melæna, circulatory collapse, and coma. The 2-year-old infant described by Simpson and Blunt [2] was already unconscious on admission only two hours after swallowing 13 g. of ferrous sulphate. Although blood-loss is rarely massive, perforation of the injured mucosa is a real danger. A misleading period of clinical improvement precedes the second phase, in which hepatic, metabolic, and cerebral injury is added to the local manifestations. This deterioration is marked by renewed restlessness, collapse, convulsions, and coma. Jaundice may be apparent, with biochemical evidence of disordered liver function. Abnormal electroencephalograms have been recorded in the acute phase [2]; fever and leucocytosis are usual; and the blood-pH and serum-bicarbonate levels are depressed, indicating metabolic acidosis.[5] Patients who recover are likely to have troublesome gastritis for a week or more; and in the third phase, about three to six weeks after the acute episode, symptoms of upper-gastrointestinal obstruction may develop owing to scarring, strictures, or pyloric stenosis. Fortunately, hepatic and cerebral functions recover without sequelæ.

Many workers have shown that prompt treatment can save life. As a first-aid measure, vomiting must be induced by passing a finger to the back of the tongue, preferably after a drink of milk. This important measure, which can be carried out by the parent before the arrival of the doctor or ambulance, is the only means of ridding the

1. Cann, H. M., Verhulst, H. L. *Amer. J. Dis. Child.* 1960, **99**, 688.
2. Simpson, K., Blunt, A. *Lancet*, 1960, ii, 1120.
3. Shafir, M. *Pediatrics*, 1961, **27**, 83.
4. American Medical Association Committee on Toxicology. *J. Amer. med. Ass.* 1959, **170**, 677.
5. Reissman, K., Coleman, T., Budai B., Moriarty, L. *Blood*, 1955, **10**, 35.
6. D'Arcy, P. F., Howard, E. M. *Lancet*, 1960, ii, 1304.

stomach of unabsorbed tablets, which are generally too large to traverse the ordinary gastric tubes. The subsequent treatment, which necessitates admission to hospital, has been set out clearly by Shafir.[3] At first, shock should be combated by means of warmth, oxygen, and intravenous fluids. Gastric lavage is repeated as soon as possible, using 1% sodium-bicarbonate solution or a 10% solution of disodium orthophosphate,[7] of which 25–50 ml. is left in the stomach. Both react with iron to form insoluble iron compounds; but sodium bicarbonate has the added merits of being readily at hand and of correcting acidosis. Calcium disodium edathamil (E.D.T.A.), a chelating agent widely used in the treatment of lead poisoning, has been shown experimentally and clinically to reduce serum-iron levels.[2 3 7] Iron is absorbed freely from the damaged mucosa; and serum-iron levels over 3000 μg. per 100 ml. (normal 40–180) are common in poisoned children, and are thought to be responsible for the severity of the systemic effects. An intravenous infusion of 500 mg. of calcium disodium edathamil in isotonic glucose solution should therefore be started as soon as possible and be continued slowly for six to twelve hours so as to reduce the levels of circulating iron, and this should be repeated daily until the patient is out of danger, or the serum-iron level is normal. Edathamil is poorly absorbed from the intestine; but similar doses may be given by mouth or into the stomach to aid the fæcal excretion of iron. Supportive measures to correct blood-loss and acidosis must not be neglected; and it may be necessary to infuse blood, edathamil, and 1/6*M* lactate simultaneously. Secondary bacterial infections, especially of the lung, must be guarded against by parenteral antibiotics. Finally, with recovery from the acute episode, the possibility of subsequent gastrointestinal obstruction should be borne in mind and the patient kept under observation.

MATERNITY IN UGANDA

In her introduction to the second clinical report from the Mulago Hospital [8] Prof. Coralie Rendle Short gives a vivid picture of maternity in the African population around Kampala. The majority of the mothers are of humble origin, coming from the small mud and wattle huts that are common in that part of Uganda. There is no domiciliary service, and unless the patient is confined in hospital she will have no skilled assistance. Hospital numbers increase each year, and overcrowding is a serious problem. A new hospital with a larger maternity section is nearing completion and should be ready for occupation in 1962. Although the mothers are aware of the benefits of hospital delivery they have not so far accepted the need for antenatal care. Many still follow the old way of life, and through ignorance or fear arrive in hospital after protracted labour, often with disastrous complications. In the three years 1956–58 there were 122 maternal deaths, and, with few exceptions, these mothers died within an hour or two of being admitted to hospital: nothing could be done for them. Spontaneous rupture of the uterus was the commonest cause of death; but hæmorrhage, sepsis, and shock took a heavy toll.

One of the chief difficulties is shortage of trained nurses. The policy in Uganda is to Africanise whenever possible; and Professor Rendle Short is rightly anxious lest standards fall, for there is still much prejudice against education for women. The few girls able to take responsible posts do not usually choose nursing. There is a pressing need for sisters and supervisors to train African staff and maintain standards.

In the Milroy lectures for 1958 [9] Dr. Cicely Williams dealt with some of the impediments to medical advance in developing countries. Social and religious customs and lack of education are often associated with ill-informed attitudes to health and nutrition. These influences are of particular importance in relation to maternity and child health. Hospitals with their advanced techniques are very necessary, but it is equally important that the doctor should study and understand the social and environmental factors that affect the life and health of patients.

It would be of great interest to hear more from Professor Rendle Short about the background to maternity in Uganda and the steps that are being taken to overcome problems of communication and education. The present report makes it clear that the maternity department at Mulago Hospital faces immense difficulties; and Professor Rendle Short and her medical and nursing colleagues deserve the highest praise for their work.

SUPPURATIVE ARTHRITIS

Infective arthritis is now far less common in hospital practice than in the days before antibiotics. Early chemotherapy produces a rapid cure and prevents arthritic complications of such infections as pneumonia, meningitis, and gonorrhœa. But when infective arthritis does develop, chemotherapy gives rise to its own problems: the bacteriological diagnosis is obscured when treatment is started before an affected joint is aspirated, and antibiotic resistance leads to further therapeutic difficulties.

Ward et al.[10] have reviewed 24 cases of suppurative arthritis treated at the Massachusetts General Hospital in 1947–57. The patients' ages ranged from 1 to 75 years, but the frequency was greatest in children and in the aged; the sex distribution was equal. In 21 cases the arthritis was monarticular and generally involved a knee-joint. The characteristic clinical features—fever, tenderness, painful limited movement, swelling, and heat, usually with effusions—were usually present, but in only 5 cases was the disorder diagnosed on admission, the commonest error being to diagnose uncomplicated rheumatoid arthritis. The joint fluid contained 25,000–253,000 leucocytes per c. mm. with over 90% polymorphs. Culture of synovial fluid was positive in 18 instances; and in 11 staphylococci were grown. The portal of infection was not always evident, but in 22 patients a hæmatogenous source was probable.

Patients whose joints are already damaged by rheumatoid arthritis seem to be especially susceptible to suppurative arthritis, and in such cases diagnosis is especially difficult. Of 25 cases of suppurative arthritis seen at Manchester Royal Infirmary between 1950 and 1957, 12 were patients with rheumatoid arthritis.[11] In many of these, suppuration had occurred in several joints; and therefore clinically the picture resembled that of an exacerbation of rheumatoid arthritis, especially since significant fever and leucocytosis were sometimes absent, or fever was already present with active rheumatoid disease. Rigors were a useful indication of infection. Unless joint aspiration led

7. Bronson, W. R., Sisson, T. C. *Amer. J. Dis. Child.* 1960, **99**, 18.
8. Clinical Report of the Department of Obstetrics, Makerere College Medical School, Kampala, Uganda, 1956-58.
9. Williams, C. D. *Lancet*, 1958, i, 863.
10. Ward, J., Cohen, A. S., Bauer, W. *Arthr. Rheum.* 1960, **3**, 522.
11. Kellgren, J. H., Ball, J., Fairbrother, R. W., Barnes, K. L. *Brit. med. J.* 1958, i, 1193.

to the correct diagnosis, large collections of pus could remain unrecognised and lead to death. Suppurative arthritis has been described by Mills et al.[12] as a complication of steriod therapy; but only 2 of the 12 Manchester patients were receiving corticosteroid therapy at the time of onset.

Intra-articular injection of hydrocortisone is another potential cause of suppurative arthritis,[13 14] but such infection is generally believed to be due to faulty technique. Certainly repeated injections—and possibly systemic steroids—may predispose to the collapse of weight-bearing joints,[15 16] but this is probably due to excessive movement of a diseased joint permitted by relief of pain (as in a Charcot joint) and not to infection. When careful asepsis is maintained, infection rarely complicates intra-articular injections.

The outcome of acute suppurative arthritis in otherwise healthy people is today generally favourable. Poor end-results seem to be more closely related in delay in starting treatment than to any other single factor.[10 17] An early diagnosis can be made only by joint aspiration, which should be undertaken as soon as the condition is suspected. Systemic administration of antibiotics effective against the particular organism usually suffices; but effusions should be repeatedly aspirated, and the opportunity can then be taken for local injection of antibiotics. Surgical drainage is rarely necessary. The joint should be immobilised in a splint until the infection has subsided, when active exercise will restore movement in a surprisingly short time.

RADIOACTIVE FOOD AND WATER

IN the investigation of man's environment and its influence upon his health, natural radioactivity has attracted much less attention than the radioactive environment devised by man himself. Nevertheless, knowledge of natural environmental radioactivity has expanded rapidly, particularly in the direction of physical measurement of the various sources of radiation, but this progress has not been matched by parallel advances in biological observation and knowledge. Biologically, the most important natural terrestrial sources of radioactivity are the radium and thorium series. Decay by alpha-emission —in view of the high relative biological efficiency of alpha particles—is of the utmost importance when natural activity is ingested in food and water.

Alpha activity in food varies tremendously: in Turner et al.'s samples,[18] the most active food (Brazil nuts) had 20,000 times the alpha activity of the least active foods. The range extended from less than 0·1 μμC per 100 g. to 1690 μμC per 100 g. in the nuts. The same foods vary from area to area, and Marsden and Green [19] have demonstrated that changes in pH of the soil produced notable changes in the alpha activity of the same strain of wheat. Among the foods more regularly eaten in this country, breakfast cereals contain the most natural radioactivity, and milk products, fruit, and vegetables are low in the list. An adequate Western diet is unlikely to contain less than 5 μμC of alpha activity per day; and exotic nutty diets may go as high as 1000 μμC.[20] No-one can yet say how many people are consuming diets of very high activity, and in view of the sparse information about tissue doses from absorbed alpha-emitters, and the very few metabolic balance studies that have been conducted, it would be easy to underestimate or even overlook the biological impact of such diets. Considering the large energy releases involved in tissue, it would be surprising if active foods had no effect at all.

The natural radioactive content of drinking-waters also varies widely. Deep-well waters are fairly active (a long-lived activity of about 0·6 μμC per litre, which is of the same order as the strontium-90 content observed in rivers and lakes in the first half of 1959 [20]); but much higher values have been recorded. Turner et al.[21] examined spa waters that went as high as 48·5 μμC per litre, and some of their Cornish samples had as much long-lived alpha activity as 9·4 μμC per litre. Values for short-lived alpha activity (excess radon and daughters) may reach much greater levels (9000–10,000 μμC per litre in the water from St. Ives); but what this signifies biologically is again uncertain. The experiments which Meyer [22] described in 1929 still seem to be the best guide to the metabolism of radon and radium, and they suggest a mean time of residence in the body of the order of 1 hour for radon. Mayneord [20] remarks, in an appendix to the Medical Research Council report, that the energy deposited by the disintegration of radon with that of its daughters could be appreciable in people drinking spa or some Cornish waters.

Turner et al.[21] also examined some specimens of West Devon water, and their findings accord with those of Abbatt et al.[23] Attention had been drawn to this area by Allen-Price's suggestion [24] that there were unexpected variations in cancer incidence (such as the Registrar General's figures have demonstrated in North Wales, particularly in Anglesey) and that a connection with water-supplies was possible. An intensive programme of further measurements (both of radioactivity and trace elements) is being conducted in West Devon, and integrated with a social survey, in an attempt to define a human population and individual exposure to radiation and to any other agents in the water. Lucas and his colleagues [25] at the Argonne National Laboratory are doing something similar in the Middle West. Certainly, the chief need for the immediate future is more information about doses received by human tissues from radioactive substances absorbed in water and food, and that involves knowing much more about what happens to these substances in all human tissues: this is primarily a question of biology and not of physics. To interpret these accumulating data it is necessary to relate them to living populations and particularly to individuals at every stage of life, and this can only be done by investigations on a wide and expensive scale. A great many small inquiries, carefully coordinated and fitted into a general overall plan, might be the most fruitful approach.

Radiation is only one factor in man's environment, and the mass of new physical details about natural radioactivity must not obscure the possible influences of other agents, such as trace elements. Indeed, the beautiful

12. Mills, L. C., Boylston, B. F., Greene, J. A., Mayer, J. H. *J. Amer. med. Ass.* 1957, **164,** 1310.
13. Gowans, J. D. C., Granieri, P. A. *New Engl. J. Med.* 1959, **261,** 502.
14. Tondreau, R. L., Hodes, P. J., Schmidt, E. R. *Amer. J. Roengenol.* 1959, **82,** 258.
15. Chandler, G. N., Wright, V. *Lancet*, 1958, ii, 661.
16. Sweetnam, D. R., Mason, R. M., Murray, R. O. *Brit. med. J.* 1960, *i*, 1392.
17. Chartier, Y., Martin, W. J., Kelly, P. J. *Ann. intern. Med.* 1959, **50,** 1462.
18. Turner, R. C., Radley, J. M., Mayneord, W. V. *Hlth Phys.* 1958, **1,** 268.
19. Marsden, E., Green, E. N. *Nature, Lond.* 1961, **189,** 326.
20. Mayneord, W. V. *in* Hazards to Man of Nuclear and Allied Radiations; p. 75. A Second Report to the Medical Research Council. H.M. Stationery Office, 1960.
21. Turner, R. C., Radley, J. M., Mayneord, W. V. *Nature, Lond.* 1961, **189,** 348.
22. Meyer, S. *Mitt. Inst. Radiumforsch. Wien.* 1929, Nr. 238.
23. Abbatt, J. D., Lakey, J. R. A., Mathias, D. J. *Lancet*, 1960, ii, 1272.
24. Allen-Price, E. D. *ibid.* 1960, i, 1235.
25. Lucas, H. F., Krause, D. P. *Radiology*, 1960, **74,** 114.

precision of physical measurements may mislead us by obscuring the present lack of balance created by deficiencies in parallel human biological and metabolic knowledge.

CHILDREN OF PSYCHOTIC PARENTS

NEUROTIC and psychotic traits are believed to be inherited independently, and the study reported by Dr. Valerie Cowie to the Section of Psychiatry of the Royal Society of Medicine on April 11 was designed to measure neuroticism in the children of psychotic parents, and thus to throw a light on the environmental effect of the psychosis. Conducted at the Genetics Unit of the Institute of Psychiatry, London (later the M.R.C. Psychiatric Genetics Research Unit), the survey examined some 330 children of psychotic patients treated in the Bethlem Royal and Maudsley Hospitals and compared them with a similar number of control children of mentally healthy patients treated in general hospitals. Ages ranged from 2 to 55, and data were derived mainly from clinical interviews with the parents, but also from a special form of teacher's report and, with older patients, a self-administered Maudsley personality inventory.

Plotting the incidence in time of neurotic symptoms showed an excess during the two years after the onset of the parental psychosis, and individual case-reports, too, often showed a causal relationship. But the overall rating for neuroticism did not differ materially between proband and control groups—a point which Dr. Cowie took to indicate the transience of environmentally precipitated childhood neuroses. Early onset, too, of affective disorder in a parent was more harmful than such disorders of late onset—further support for the environmental hypothesis. Of the various diagnostic groups, the small number of obsessive-compulsive parents (of either sex) produced the highest proportion of disturbed children—over-dependent, faddy, and prone to tantrums, but generally not obsessional themselves.

Regarding the age at which damage was greatest, parental psychosis when the child was under 2 seemed to produce no excess of neurotic features; and though in the 3–5 group the incidence was higher, it did not reach significance. The sex of the parent mattered most with schizophrenia, for while a schizophrenic father did little damage, such mothers were associated with adverse circumstances more than any other group studied.

Perhaps the most important suggestion from this work is that community care of the psychotic may be a lot less harmful to others than one might expect—supporting, as Dr. A. A. Baker pointed out, a clinical impression many had held. His unit for mothers and children had shown that even a mother in catatonic stupor or excitement could feed a baby on the breast; and discharged schizophrenics (who never, in his view, needed to be separated from their children) seemed to make rather better mothers than discharged neurotics.

But Dr. Cowie and others (notably Dr. John Bowlby) pointed to some inevitable shortcomings in design: the control group was not a random population, the age-range of probands was very great, and the validity of much of the data—particularly the retrospective data—could be questioned. Furthermore, the duration of the psychosis, the degree of manifest disturbance, and the length of contact between parent and child were not recorded. As Dr. Bowlby said, one really needs a careful study at the time of the calamity and thereafter, but this would be difficult.

It is too soon to dismiss possible unfortunate social consequences of the large-scale discharge of chronic patients, as feared by Professor Titmuss,[1] but some of the auguries are hopeful.

McARDLE'S SYNDROME

IN 1951 McArdle [2] described the case of a patient who had a hitherto unrecognised form of myopathy which was apparently due to a defect in muscle-glycogen breakdown. The patient's principal complaints were of pain and stiffness in all the voluntary muscles following even moderate exertion. The symptoms had been present from early childhood, but by severely restricting his muscular activity the patient had learnt to live with his disability. A similar case was reported by Schmid and Mahler [3] in 1959, but in this case the clinical manifestations became increasingly severe after adolescence; severe muscular cramps, often accompanied by transient myoglobinuria, were followed by weakness and wasting of muscles in the trunk and limbs. Biochemical investigations on specimens of muscle obtained by biopsy revealed that the glycogen content of the muscle was greatly increased (though glycogen could be synthesised from uridine diphosphate glucose in vitro), that conversion of glycogen to lactate in vitro was greatly reduced, and that all phosphorylase activity was absent. The activity of other glycogenolytic enzymes was normal. Pearson [4] has since described another case of the condition; the clinical history was similar to that given by McArdle's patient, in that severe muscular pain, stiffness, and even local swelling followed moderate exertion. Graduated exercises on a treadmill revealed very poor exercise tolerance, but this could be greatly improved by continuous intravenous infusion of glucose. In this case histochemical examination of a biopsy specimen of muscle confirmed that all the muscle-fibres were loaded with glycogen and that phosphorylases a and b were absent. Whereas each of the cases hitherto reported has been sporadic, Schmid and Hammaker [5] now describe three cases in a single sibship, and suggest that this disorder is probably genetically determined and that it is due to an autosomal recessive gene. They found that some symptomatic improvement followed thrice-daily intramuscular injections of glycagon.

Probably the condition, though rare, is commoner than is generally realised. It should be considered in all patients complaining of generalised muscular pain and cramps following slight or moderate exercise, particularly if the symptoms date back to early childhood. Very possibly some patients diagnosed as cases of myotonia paradoxa [6] and some with paroxysmal myoglobinuria [7] may have this syndrome, which appears to represent yet another type of glycogen-storage disease,[8] involving specifically the skeletal muscles.

Mr. JULIAN TAYLOR, consulting surgeon to University College Hospital, London, and the National Hospital, Queen Square, and a former professor of surgery at the University of Khartoum, died on April 15 aged 72.

1. Titmuss, R. M. Address to annual meeting of National Association for Mental Health, March 10, 1961. See *Lancet*, March 18, 1961, p. 608.
2. McArdle, B. *Clin. Sci.* 1951, **10**, 13.
3. Schmid, R., Mahler, R. *J. clin. Invest.* 1959, **38**, 2044.
4. Pearson, C. See *Lancet*, Feb. 4, 1961, p. 276.
5. Schmid, R., Hammaker, L. *New Engl. J. Med.* 1961, **264**, 223.
6. Marshall, J. *J. Neurol. Psychiat.* 1952, **15**, 206.
7. Hed, R. Myoglobinuria in Man. Stockholm, 1955.
8. See *Lancet*, Jan. 28, 1961, p. 206.

Occasional Survey

THE MATERNITY SERVICES

Need for Changes in Attitude and Practice

THOUGH much safer than formerly, our maternity services have ceased to be our pride and joy. Some maternity hospitals are so overcrowded and their staff are so overworked that they are resorting to practices which are barely tolerable. Nor is this a problem that will solve itself. In two or three years' time the big post-war generation will be requiring maternity beds—several years before it begins to furnish pupil midwives. Some think that, under the weight of this last straw, the services will break down unless they are strengthened quickly.

RECENT CRITICISMS

Perhaps because overwork leads to an impersonal attitude, public complaint has so far been mostly of "inhumanity". A professor of obstetrics was "shocked, horrified, depressed" at the experiences of mothers in hospitals [1] and Professor Nixon has described many hospitals in this country as "inhuman to mothers".[2] During the past few years articles on this topic have appeared in the press, and letters from dissatisfied mothers have been read out on the air. An Association for Improvements in the Maternity Services [3] has recently been formed which, among other aims, sets out "to banish, through influence, the dark-age attitude towards the psychology of childbirth" and "to eliminate all unnecessary suffering in childbirth". At the same time, articles in professional journals have drawn attention to undesirable attitudes and practices and to the need for change.[4 5]

The Cranbrook report [6] noted "a general complaint that there was in many hospitals too little regard for the personal dignity and emotional condition of women during pregnancy and childbirth". Women were sometimes left too long alone in labour; the staff were said to be sometimes too busy to bother about analgesia; and mention was made of noise and disturbance and of too much or too little privacy. Recently some complaints have been more extreme.[1 7] Mothers have said that childbirth was "a nightmare experience" and that they were attended by midwives "who were entirely without kindness or even courtesy". Hospitals are criticised for their rigid routines and unnecessary rules. It is said that "natural childbirth" methods advocated by antenatal clinics are frowned on in the labour wards. Long waits in antenatal clinics and unimaginative nursing care after delivery are also commonly spoken of.

Most of this criticism is directed at hospitals. Many mothers compare their reception and management in hospital unfavourably with confinement at home.[8] Of one series of 336 mothers who had had at least one baby born in hospital and one at home, 80% preferred home confinement and only 14% hospital confinement.[9]

How widespread this dissatisfaction may be is not known. The Cranbrook report [6] emphasises that the majority of women questioned by the committee appeared to be satisfied with the maternity services. In a recent survey,[10] when mothers were questioned about the welfare services they had used, only 4% expressed dissatisfaction with the midwives—a proportion lower than for any other welfare service except that of home nurse.

Much of the criticism is hard to evaluate. Complaints such as "I was just one more nuisance, particularly as I arrived at 10 P.M. and, although nurses work by night, they must on no account be disturbed" [1 7] are difficult to take seriously. A statement such as "left entirely alone for first stages of labour (eleven hours)" [1 7] must, under any hospital system, be an exaggeration. But, even when allowances have been made, there remains a hard core of complaints which many people—both inside the professions and outside—believe to be justified. Unquestionably, many modern mothers do suffer as a result of "conveyor belt" methods. They like to know what is happening to them and what to expect. When in labour they do not want to be left for long hours alone, particularly if nobody answers the bell. They suffer if there are differences of opinion and personal conflicts among those who look after them, and also if there is lack of sympathy. All professions have a few unsuitable people in their ranks, and midwifery is one where such people can cause an exceptional amount of suffering.

Moreover, at a time when most midwives are overworked, patients have changed. As economic standards rise, emotional problems become more and more important, and there is likely to be anxiety about the outcome of pregnancy. Emotional aspects of pregnancy, and the stresses which may appear in the family group as a result, are much more obtrusive.[11] The cultural pattern of the modern maternity unit may be alien to the woman who is bearing a child.[12] Women develop the idea that childbirth is their moment of greatest achievement and sometimes of greatest happiness. It becomes an immensely significant emotional as well as physical event.[5] A woman who does not have these feelings may think she has been mishandled or "deprived". During the last few decades there has been a striking change in what mothers know and wish to know about pregnancy and childbirth, and also in their attitudes to the medical and nursing professions. Many are far better informed about the functions of their bodies and will no longer blindly follow the advice given. They question what they are told. If any abnormality arises they want to have an explanation of its meaning. Advice not to worry may make them feel that information is being withheld.[8]

But despite these tremendous changes affecting so many young mothers, maternity units often remain relatively unchanged in organisation and attitudes. Childbirth is now physically safe, yet the chief emphasis is still on mechanistic midwifery.[13] It has even been suggested that undue concentration on the mechanical aspects of obstetrics has sometimes diverted attention from the patient's general health so that it has actually contributed to avoidable maternal deaths.[14] It also tends to override important psychological and emotional considerations.

1. B.B.C. Network Three: Parents and Children. Jan. 2, 1961.
2. Nixon, W. C. W. See *Lancet*, April 8, 1961, p. 765.
3. A.I.M.S., 1, Batchwood Gardens, St. Albans, Hertfordshire.
4. Rayner, C. *Nursing Times*, Sept. 9, 1960, p. 1124.
5. Morris, N. *Lancet*, 1960, i, 913.
6. Ministry of Health: Report of the Maternity Services Committee. H.M. Stationery Office, 1959.
7. Soward, J. *Guardian*, Jan. 18, 1961.
8. Ministry of Health: Central Health Services Advisory Council. Standing Maternity and Midwifery Advisory Committee. Human Relations in Obstetrics. H.M. Stationery Office, 1961. Pp. 5. Price 6*d*.
9. Gordon, I., Elias-Jones, T. F. *Brit. med. J.* 1960, ii, 52.
10. P.E.P. Family Needs and the Social Services. London, 1961.
11. *Wld Hlth Org. techn. Rep. Ser.* 1952, no. 51.
12. Tylden, E. *Lancet*, 1952, i, 231.
13. Nixon, W. C. W. *ibid.* 1961, i, 765.
14. Ministry of Health. Report on Confidential Enquiries into Maternal Deaths in England and Wales 1955–57. *Rep. publ. Hlth med. Subj. Lond.* 1960, no. 103.

OVERCROWDING

Hospitals are already delivering 40% more babies than they were five years ago, and there is a disquieting shortage of midwives.[6 8 15–20] Here there is evidently a vicious circle, since the chief deterrent to the practice of midwifery in hospitals seems to be the high pressure of work.[18] Pupil midwives tend to be put off: practising midwives become bewildered and unhappy.

Some hospitals are forced to find their own solutions to the problem of overcrowding. In some areas patients whose home conditions are unsuitable for delivery are given only a provisional hospital booking. If the wards are full when they arrive in labour, they are transferred to another hospital. Yet anxiety in pregnancy due to uncertainty as to where the baby will be born can be very distressing. Even worse in its effects is the practice in London of referring these patients to their own doctors, who must visit them when they go into labour and then ask the Emergency Bed Service to accept them as emergencies. Sometimes the baby is born while all this is being arranged. There have been protests about this system in the journals,[21] but every year more and more patients become " emergencies " in this way. During the year ended March 31, 1961, the London Emergency Bed Service dealt with 3263 obstetric emergencies, of which more than half were emergencies only because they had been unable to find beds. The corresponding figures for the previous year was 2693 and for the year ended March 31, 1958, 1699. Five years ago this practice was virtually unknown.

ERRORS OF ATTITUDE?

At best, these arrangements are poor and makeshift. If they are allowed to continue they will become a public disgrace.

Many of the present shortcomings in the maternity services, including at least some of the overwork, can be attributed to lack of communication leading to mutual misunderstanding, vicious circles, and poor human relations. There is often lack of cooperation and understanding, and sometimes even hostility, between doctors and midwives, between individuals working in the same unit, and between the hospital, the general practitioners, and the public-health authorities. An authoritarian attitude is sometimes taken by doctors and midwives when a permissive one would be more appropriate and effective.[22] There may be a tendency to jealousy or possessiveness. Sometimes there seems to be failure by the mother to express her needs and by doctors and midwives to satisfy them. There is also an unwillingness to concede that " lay " people may make a useful contribution.

Perhaps the training of nurses and midwives perpetuates this lack of communication. A supervisor of midwives has suggested that some of the unkindness, impoliteness, and poor work found in the midwifery profession is a carry-over from earlier training.[23] Morris [5] has noted that nurses in training always seem to be walking about and are seldom encouraged to sit down and talk to their patients: does this, he asks, also contribute to the later development of an inhuman attitude? A recent report [24] suggests that nursing practice sometimes lags behind medical advances, and that nurses are inclined to cling to traditional practices which are not always compatible with modern methods of treatment. Superimposed on this conservatism is the problem of shorter working hours for hospital staff. It is felt that in some instances shorter hours have been introduced at the expense of the patient's welfare.

There is widespread agreement about what in general should be done; but practical suggestions as to *how* it should be done are fewer and often conflict.

TRAINING OF DOCTORS AND MIDWIVES

Various suggestions have been made about the training of doctors and midwives. Nurses now receive tuition in psychology as part of their general training, and it has been proposed that pupil midwives should receive further training in psychology and its relation to maternity. For many years the Central Midwives' Board has emphasised the importance of promoting a happy and serene attitude in the mind of the patient. Their pamphlet of suggestions and instructions [25] is now being revised and will probably contain more about patients' emotional needs.

Definite suggestions as to what and how pupil midwives should be taught in psychological matters have been made by Dr. Elizabeth Tylden.[26] She believes that the syllabus—of which she presents a draft—should include a good deal about the psychology of pregnancy and childbearing, including the midwife's own emotional attitudes. This is an important suggestion but also a controversial one. Her object is to make the future midwife aware of the emotions she will be handling, which seems reasonable enough. On the other hand, a little learning of this kind is not going to make unsuitable people into good midwives; and, since pupil midwives and those who teach them are, on the whole, practical people, it might be better to confine the teaching to more practical matters. Kindness and understanding taught by practical suggestions, and above all by example, may, in our present state of knowledge, be more effective than theoretical instruction in " human relations " and " insight ". This applies to the teaching of medical students as much as to pupil midwives.

In a busy maternity department the patients' contentment, and their sense of personal satisfaction or failure, often depend largely on the pupil midwives and medical students who attend them. The value of the part that these pupils and students play depends in turn on the attitude of their teachers and on how their courses are organised. In some teaching hospitals both pupil midwives and medical students are allotted their patients when these are first admitted—in early labour, if not before. Thenceforward it is the personal responsibility of the pupil or the student to spend as much time as possible with the patient, to encourage her throughout her labour, to allay her fears and anxieties, to give her confidence in her body and in her surroundings, to deliver her baby, and to study and care for her during the lying-in period. Managed in this way, the whole process can be of enormous value to both patient and student. The student learns that the mechanistic aspects of labour are only one small part of a series of fascinating physiological, psychological, and biochemical changes

15. *Lancet*, 1961, i, 234.
16. *Nursing Times*, Sept. 30, 1960.
17. Wood, A. *Midwives' Chronicle*, 1961, 74, 39. (Feb.)
18. Ministry of Health circular H.M. (59) 80.
19. Ministry of Health circular H.M. (59) 10.
20. Ministry of Health circular H.M. (61) 5.
21. Abercrombie, G. F. *Lancet*, 1959, ii, 398; *Lancet*, 1959, ii, 392; Darnley, J. C. *Brit. med. J.* 1959, ii, 951; *Brit. med. J.* 1959, ii, Suppl. p. 151; Ellison, S. *Brit. med. J.* 1960, i, 378.
22. Royal College of Midwives. Report of the Conference on Human Relationships in the care of Mother and Baby. 1960.
23. Entwhistle, E. R. *Nursing Times*. Sept. 30, 1960. p. 1211.
24. Ministry of Health: Central Health Services Council. The Pattern of the In-Patient's Day. H.M. Stationery Office. 1961. Pp. 27. 2s.
25. Central Midwives Board: Suggestions and Instructions Regarding the Conduct of the Course of Training of Pupil-Midwives. 1955.
26. Tylden, E. *Midwives' Chronicle*, March, 1961, p. 92.

about which we still have much to learn. A humanitarian attitude should develop automatically under such a regime.

Unfortunately there are still teaching units where the study of the first stages of labour and attention to the patient's needs at this time are not encouraged. Patients are not allotted to the student or pupil until the os is fully dilated, and the study of midwifery is degraded into little more than catching the baby and witnessing as many abnormal modes of delivery as possible. Such a system seems likely to have a dehumanising influence, which may last.

Practical instruction can also be given in the psychological management of patients in labour, including those who are emotional or " difficult ". It is easy to demonstrate that women in labour are easily upset and that a " tit for tat " attitude towards them when they appear to be unreasonable is quite valueless.

TRAINING THE PATIENTS

Some regard training the mother as just as important as training the midwife. Such training usually involves lectures, a course of antenatal exercises, some form of psychological preparation, or a combination of these. But, though it has helped very many mothers to have tolerable or enjoyable labours, many obstetricians are not convinced that the methods used are beneficial to all patients, or even that they are free from harm.[27] It may be that these ideas can adversely affect those whom the methods fail to help. Particularly suspect is the suggestion that women can be trained in these methods by post and by reading books. Subsequent failure and disappointment may result in a good deal of mental distress—and possibly in complaints against the maternity services.

Nevertheless most obstetricians and midwives would probably agree that the ability to relax, both during uterine contractions and between them, is a valuable asset to a woman in labour. Further research is needed into how this might be achieved more widely. At the moment there is little agreement. It is not even known whether poor attendance at antenatal classes, which has deterred some hospitals from organising them, is due to bad organisation and teaching or to the fact that many expectant mothers do not wish to attend courses during pregnancy. Certainly there are obstetricians who hold that such classes are valueless, just as there are mothers who prefer a few hours of pain to spending several hours a week during pregnancy in preparing to avoid it.

The value of health education is now widely accepted [8 14 22 28]; but ignorance and misunderstanding are not always due to lack of antenatal education. Serious anxiety and misunderstanding can indeed be caused by misunderstood antenatal lectures. For instance, after a lecture on the placenta, one mother was left supposing that the baby breathed through her own umbilicus—and suffered agonies thinking she had drowned her baby in the bath.[4] Another mother, hearing that the head is born first, followed by the body, was worried lest the doctor should be unable to stick them together again. An important aspect of antenatal training is to make sure that the patient does not misconstrue what is said, and that she understands that the maternity services exist for her safety as well as for her comfort.

ANTENATAL CLINICS

Antenatal clinics are a source of complaint. Their size and the necessity for efficient organisation can easily produce an inhuman atmosphere and sometimes long waits. Appointment systems can be very helpful, but in some areas patients are very lax about keeping to them. Clinics are often drab, colourless, uncomfortable, and unfriendly [5] and often there is nobody who can give the patient enough time to let her ask the questions that worry her. The suggestion has been made that busy clinics should have at least one midwife or doctor whose prime duty is to answer patients' questions, and to give them every opportunity to ask.

LABOUR WARD PROCEDURE

Criticism has also been made [5] of the ceremonial known as " being admitted " to which a patient is submitted when she arrives at hospital in labour. After supplying " particulars " to a porter or nurse, she is undressed, shaved, and given an enema and a bath, and maybe some castor oil, too. She may be dressed in a garment reaching only to her waist, in which she is expected to walk about. Hence it is not surprising that there have been many complaints about the indignity and discomfort of admission to a labour ward. Yet suppositories may be as effective as enemas and also save some of the pupil midwife's valuable time. There seems no reason why labour-ward garments should not be made of at least a decent length.

Having been admitted, the woman may be put into a first-stage room with other mothers in labour, or else into the general ward. Many women have found this experience unnerving. Even more frightening is the experience of being left alone for many hours at a time, being visited only for essential purposes. In some hospitals there are day-rooms where patients in the first stage of labour can sit comfortably, walk about, watch television, and talk to their husbands. An increasing number of hospitals allow husbands to remain with their wives throughout the first stage of labour and often during the second, too. This practice is widely regarded as beneficial where both husband and wife wish it,[5 8] and a recent lively correspondence in the *British Medical Journal* has canvassed both advantages and disadvantages.[29] Another scheme for women whose husbands are not available is the use of lay helpers to sit with women in labour. This has not met with as much approval from the profession as has the presence of husbands or even mothers. Doubt has been expressed about the motives and psychological state of the women who wish to do this work.

Serious consideration of the problems of pain, and in particular its connection with fear, is desirable for all who work with women during pregnancy and labour. The ways in which fear, anxiety, and guilt can affect a woman's reaction to pain can be easily demonstrated, as can the beneficial effects of maintaining physical comfort and personal dignity. There still seem to be pupils and students, and even doctors and midwives, who are unaware that palpation that is performed roughly or with cold hands or during a contraction can upset the patient considerably—as can any handling, moving, or turning during a pain. Labour-ward beds are another common source of discomfort. Recently a consultant obstetrician decided to spend what remained of a broken night, sleeping on an empty bed in the labour ward—and was astonished that anyone was expected to relax on it, let

27. *Lancet*, April 8, 1961, p. 765.
28. *Wld. Hlth. Org. techn. Rep. Ser.* 1951, no. 31.
29. Patterson, J. H., Burne, B. H., Davis, A. *Brit. med. J.* 1961, i, 594; Jarrett, R. J., Davies, G. L., Taylor, J. *ibid.* p. 744; McIver, K. E., Halliday, E. M., Naylor, P. *ibid.* p. 903; Kidd, H. B., Spratt, N. A. *ibid.* p. 1038.

alone women in labour. Sometimes delivery beds are so narrow that the patient fears she will fall. Others find that being made to lie flat, and being forced to turn over as the head crowns, greatly increase the discomfort. There seems to be no evidence that these procedures, any more than hard or narrow beds, are anything more than traditional in the maternity ward.

In district midwifery a healthy baby is usually given to its mother during the third stage of labour. Often it is put to the breast on the grounds that its sucking stimulates uterine contractions and helps to establish breast feeding. But in hospital, it seems, the baby is sometimes quickly removed, even when its condition is good, on the grounds that it will be in the way or that the mother must not see it until it has been cleaned and bathed. (Incidentally, a baby is likely to be much cleaner, bacteriologically, before it is bathed than afterwards.) Furthermore, it is not always recognised that many mothers become very worried if their babies do not cry at birth. If the baby's condition is not sufficiently good for it to be given to the mother immediately, adequate explanation or reassurance is necessary. Only too often the baby is whisked away without comment and the mother is left wet, cold, and worried. The fact that patients with perineal tears not infrequently complain that they suffered extreme pain while being stitched, and have had many troubles as a result, suggests that enough attention is not always paid to the technique of painless and efficient perineal suture.

PUERPERIUM

During the puerperium much of the dissatisfaction seems concerned with ward routine—noise, being awakened unnecessarily early, and so on. The puerperal woman is exceptionally sensitive, especially regarding her baby. She may worry inordinately because it has red marks or " flat feet " or does not gain weight. Sympathetic treatment can often avert the " postpartum blues ", whereas a thoughtless remark can make them much worse. A dogmatic attitude towards breast feeding can lead to unhappiness and guilt in those who are not successful.

ORGANISATION

At least some of the overcrowding and overwork is due to poor organisation more than to any fundamental need. Rowarth [30] has expressed the view that the maternity service in this country does not lack beds and facilities so much as organisation. This leads to near-chaos, overwork, and lack of coherent purpose, and also to frustration in the staff. The patient meets this when she cannot get a bed in hospital or when the hospital staff appear to be indifferent or discourteous. Rowarth believes that there are enough hospital beds for all who need them, but at present almost half are occupied by women who do not need them.[30] In Swindon, he has solved the problem by cooperation between the hospital and domiciliary services. Many will agree that lack of cooperation under the present tripartite arrangement is the cause of much of the difficulty, as is the fact that no area has anyone who is actually *responsible* for the maternity services.

ADMINISTRATION

Lack of perception has also been blamed for the overcrowding.[23] Although the Royal College of Midwives urged long ago that auxiliary staff should be employed to relieve midwives and pupil midwives of duties which can be done equally well by less skilled people, there is a good deal of evidence that midwives are still being used for domestic work or in work more appropriate to the administrative or other grades of hospital staff.[18–20 24] In one hospital the duties of pupil midwives include oiling the ward trolleys; in another, a staff midwife spends a morning each week cleaning cupboards and bowls, and a domestic worker's offer to work extra hours has been refused. In many antenatal clinics midwives do clerical work, even where other help is to be had. The most serious shortages are not uniformly encountered in the hospitals which might be thought to be unfavourably placed from the standpoint of recruitment.[19] Sometimes the trouble seems to be the low staffing allocation, since for this purpose babies, unless they are in premature units, are not regarded as patients. Good teamwork in obstetrics is essential. It is much more likely to be possible if working conditions are reasonable.

EARLY DISCHARGE

Another method of relieving hospital maternity wards while yet delivering all the women who need beds is to keep them for less than the ten-day period recommended by the Cranbrook Committee.[6] Interest in this is widespread and different methods are being tried in various hospitals. There are advantages for both patient and hospital: less work in the lying-in ward means less work for midwives or enables the hospital to rearrange its organisation, centring on the labour ward, which can thus have more staff and more facilities and therefore be more humane to patients. From the patient's standpoint, it cuts down antagonism and greatly reduces the likelihood of her becoming unhappy while in hospital. It seems that separation from home, husband, and family is the strongest reason for women's unhappiness in hospital, no matter how efficient or humane confinement might become.[9] The thought that she is being admitted only for the labour does much to mitigate this. It also saves the baby from exposure to hospital infection. One hospital [31] found that it was better to discharge suitable women on the second day, if possible, rather than send them home between the fourth and sixth days. Lactation, it is thought, should be established in one place or the other and that the mother should not be moved in the middle of it.

In many cases, the disadvantages of early discharge seem to be largely administrative. The regulation that women should be cared for by midwives until at least the tenth day of the puerperium is no doubt a good one; but domiciliary midwives often have no time to take on patients who have been delivered in hospital. Moreover, many of them dislike undertaking maternity care of a large number of patients for whose delivery they have had no responsibility.[6] Another objection is that if the lying-in wards are empty the pupil midwives will not get enough experience in nursing in them. But in hospitals where early discharge is the rule it has been found that enough patients remain in hospital for the full length of time to give the nurses the experience they need. Another suggestion has been to send pupil midwives out to nurse discharged patients in their own homes. In another hospital district midwives have sometimes been allowed to deliver their patients in the labour wards and go home with them afterwards. Yet another suggestion has been " a short stay general practitioner unit attached to a maternity hospital " in which the mother's own doctor

30. Rowarth, G. *Nursing Times*, Oct. 28, 1960, p. 1350.

31. Theobald, G. W. *Brit. med. J.* 1959, ii, 1364.

and midwife would look after her during labour and after her early discharge home. One obstetrician estimates that such a scheme would empty at least half his beds. Early discharge is suggested, possibly within twenty-four hours of delivery.[32]

PART-TIME STAFF

An increasing use of part-time staff is in keeping with modern trends and could do much to overcome the shortage of midwives. In some quarters there is persisting opposition to the wider use of part-time staff. Even where hospitals have introduced part-time staff, this is sometimes attributed more to expediency than to conviction that they are a valuable addition to the ward team.[24] Because women are marrying younger and almost none of them are remaining single, the hospitals of the future, like the schools, will be staffed largely by part-timers or not at all. And whether or not they will come to work at all will depend on the conditions of work.

Of the 70,000 women on the Midwives' Roll, about 20,000 have ceased to practise, usually for domestic reasons. Many of these might be prepared to return to practice if working conditions and hours of duty could be arranged to suit their circumstances. The Central Midwives' Board has drawn up local lists of midwives not in practice and will give these lists to hospital authorities to use in their efforts to attract midwives back to practice.[20] Probably, too, much of the work at present done by midwives could in fact be done by assistant nurses, nursing auxiliaries, nursery nurses, and domestic workers.[18 19]

The more imaginative use of part-time staff in domiciliary practice might also do much to relieve the pressure and congestion on the maternity hospitals. There are many married midwives and nurses who are not in a position to undertake work that is full-time or irregular in hours. Moreover, domiciliary work attracts many midwives who would not in fact practise at all if they had to work in a hospital.[6] It seems likely therefore that there are trained midwives not at present working who would be pleased to work for a few hours a day caring for lying-in mothers in their homes after delivery in hospital. Most of these midwives would have families of their own and would be particularly suitable in helping the mothers to settle at home with their new babies. It might also be possible to train older women—not necessarily already nurses—to do this work, provided the necessary courses of instruction are arranged in a way that will suit their other commitments.[33]

CONCLUSIONS

The problem of combining the efficiency of the conveyor belt with individual attention in the presence of staff shortages can be found in most aspects of modern life. As far as the maternity services are concerned, its solution probably depends on recognising the changes that have taken place in the last twenty-five years—economic, social, psychological, and medical—and using them to plan for the further increase in the birth-rate which we know is coming. Childbirth has become and is becoming an important experience which can also, under suitable conditions, be enjoyable, and women are demanding that it be made so. Despite the difficulties, it is our responsibility to see that this becomes a reality and not a nightmare or a calamity.

32. Sluglett, J., Walker, S., *Lancet*, 1956, i, 684.
33. *Midwives' Chronicle*, March, 1961, pp. 74, 89.

Needs and Beds

THE DEMAND ON PROVINCIAL CHILDREN'S HOSPITALS

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WE have repeatedly heard the statement that the work of children's hospitals is declining. Gairdner (1956), under the impressive title "the decline and fall in hospital pædiatrics", discussed the falling demand for children's beds in the Cambridge area, and ascribed it to a rising standard of infant care, the falling incidence of gastro-enteritis and tuberculosis, and the development of antibacterial drugs. On the other hand, Taylor and Davison (1959) did not find a fall in the number of children's beds needed in the Newcastle area.

Although it is clear that the character of the work of children's hospitals may have changed, because of the factors mentioned by Gairdner, the development of more methods of investigation and treatment, and the newer surgical techniques for children previously considered to be hopeless, would make it unlikely that Gairdner's experience would be generally applicable. In addition, the increased number of children in post-war years might well be expected to increase the strain on children's hospital and children's unit accommodation.

Because of the eager acceptance of Gairdner's figures in certain quarters, and because the Cambridge experience is so very different from that at Sheffield, we decided to investigate the problem in other parts of the country, outside London. We excluded London because of the numerous children's hospitals and children's units, and because we thought that the shift of the population away from the centre would confuse the picture.

SCOPE OF THE STUDY

We decided to confine our attention to children's hospitals because of the immense difficulty and virtual impossibility of obtaining information from almost every hospital in the country concerning the number of children admitted or seen in the outpatient department. Accordingly we wrote or spoke to consultant pædiatricians, secretaries, or superintendents of the following children's hospitals, asking for their hospital statistics:

Glasgow—Royal Hospital for Sick Children.
Aberdeen—Royal Aberdeen Hospital for Sick Children.
Edinburgh—Royal Hospital for Sick Children.
Newcastle upon Tyne—Fleming Hospital; Babies' Hospital.
Sunderland—Children's Hospital.
Stockton—Children's Hospital.
Liverpool—Royal Liverpool Children's Hospital; Alder Hey Hospital.
Manchester—Duchess of York Hospital for Babies; Royal Manchester Children's Hospital; Pendlebury Hospital.
Sheffield—Children's Hospital.
Bradford—Children's Hospital.
Derby—Children's Hospital.
Hull—Children's Hospital.
Birmingham—Children's Hospital.
Nottingham—Children's Hospital.
Norwich—Jenny Lind Hospital for Children.
Bristol—Royal Hospital for Sick Children.
Southampton—Children's Hospital.
Brighton—Royal Alexandra Hospital.

If we have inadvertently omitted any children's hospital, we apologise.

We excluded the following:

1. The Children's Hospital at Hull, because the pædiatrician, Dr. M. G. Philpott, wrote that the figures would be meaningless owing to the intimate relationship between admissions to the hospital and the beds in the children's wards of the general hospital.

2. The Children's Hospital at Stockton, because it was opened during our study.

3. The figures for the outpatients at the Fleming Hospital, Newcastle upon Tyne, because the pædiatrician, Dr. G. Davison, thought that they were not reliable for part of the period.

4. The admissions to the Southampton Children's Hospital, because the wards were temporarily closed during 1958–59.

5. Outpatient figures at Glasgow, because it was not possible to separate them from casualties for part of the period.

6. Casualties. These will be mentioned separately.

In any hospital there are apt to be temporary variations in the number of beds available, because of ward closures

TABLE I—ADMISSIONS TO NINETEEN PROVINCIAL CHILDREN'S HOSPITALS

Year	Total admissions	Annual admissions (% of 1950 total)
1950	65,385	100
1951	67,976	104
1952	73,884	112
1953	78,316	119
1954	77,097	118
1955	77,051	116
1956	78,392	120
1957	78,586	120
1958	80,258	121
1959	83,184	127

on account of infection, shortage of nurses, decoration, or stuctural alterations, so that in many instances children may have been diverted to children's units of general hospitals. We believe, however, that the figures given will provide an accurate basis for studying the use to which children's hospitals have been put.

RESULTS

In table I we show the total annual admissions to nineteen provincial children's hospitals for 1950–59. It will be seen that there was an overall increase of almost 18,000 admissions in the period. In table II we show the number of admissions to individual hospitals in 1959 as a percentage of those admitted in 1950. It will be seen that in many hospitals the increase was considerable. Four hospitals showed a slight decrease in the number of

TABLE II—1959 INPATIENTS AS A PERCENTAGE OF 1950 INPATIENTS

Glasgow	138	Sheffield	178
Aberdeen	118	Bradford	135
Edinburgh	117	Derby	127
Newcastle (Fleming Hospital)	95	Birmingham	145
Newcastle (Babies' Hospital)	95	Nottingham	86
Sunderland	127	Norwich	110
Liverpool (Alder Hey)	131 } 134	Bristol	156
Liverpool (Myrtle Street)	145 }	Brighton	127
Manchester (Duchess of York)	127		
Manchester (Pendlebury)	97 } 116		
Manchester (Booth Hall)	135 }		

admissions. There were local reasons for this. For instance, in one hospital there was a change in the policy towards tonsillectomy during the period, with a consequent considerable fall in the number of admissions. In table III we show the number of admissions to hospitals in 1959 as a percentage of those admitted in 1947. These are the only hospitals for which we had the early figures. It will be seen that the increase in the number of admissions from 1947 to 1959 was much greater than that from 1950 to 1959.

TABLE III—1959 ADMISSIONS AS A PERCENTAGE OF 1947 ADMISSIONS

Glasgow	155	Sheffield	202
Aberdeen	136	Bradford	131
Manchester (Duchess of York)	186 } 127	Birmingham	106
Manchester (Pendlebury)	146 }		
Manchester (Booth Hall)	104 }		

In the Children's Hospital, Sheffield, there were just over twice as many admissions in 1959 as there were in 1947, though the number of beds available is smaller now than it was at the beginning of the period. In 1947 the total number of admissions was 2942: in 1959 there were 5935. At the Duchess of York Hospital, Manchester, in 1947 there were 1053; in 1959 there were 1961.

We could not include the figures for the Children's Hospital, Stockton, in the table, because the hospital opened during our study. In 1951 the total number of admissions was 286. In 1959 there were 1349.

It will be seen from tables IV and V that there was a corresponding increase in the number of new outpatient consultations between 1952 and 1959, the overall increase in this period being 12,340. The largest increases were at the Children's Hospital, Derby, and the Booth Hall Hospital, Manchester. Owing to incompleteness of earlier figures we were not able to include the years 1947–51 in table IV. The following particularly striking increases during the period 1947–59 are worthy of note:

At the Derby Children's Hospital the total number of new outpatient consultations in 1947 was 1241: in 1959 it was 5616. At the Booth Hall Hospital, Manchester, the total number of new outpatient consultations in 1950 was 3483: in 1959 it was 8581. The corresponding figures for the

TABLE IV—NEW OUTPATIENT ATTENDANCES IN SEVENTEEN PROVINCIAL HOSPITALS 1952–59

Year	Total	Annual total (% of 1952 total)
1952	95,516	100
1953	100,423	105
1954	99,651	104
1955	100,292	105
1956	100,912	106
1957	104,126	109
1958	107,355	111
1959	107,856	113

Children's Hospital, Aberdeen, were 6266 (in 1950) and 11,743 (in 1959).

Six hospitals showed a decrease in the number of new outpatient consultations in the period, mostly for special local reasons. For instance, in one of the hospitals there was a long waiting period for an outpatient appointment, while in an adult hospital with a pædiatric unit there was no waiting period at all, and consequently an effort was made to redistribute the outpatient load between the two hospitals.

We have not provided figures for new casualty attendances, because of incompleteness of records. For those

TABLE V—1959 NEW OUTPATIENTS AS A PERCENTAGE OF THOSE IN 1952

Aberdeen	120	Sheffield	138
Edinburgh	112	Bradford	70
Sunderland	114	Derby	229
Liverpool (Alder Hey)	119 } 109	Birmingham	102
Liverpool (Myrtle Street)	90 }	Nottingham	98
Manchester (Duchess of York)	136	Norwich	121
Manchester (Pendlebury)	73 } 114	Bristol	105
Manchester (Booth Hall)	209 }	Southampton	83
		Brighton	92

hospitals for which we have adequate figures the increase in casualty work has been striking.

In the Derby Children's Hospital the total number of new attendances in 1947 was 1974: in 1959 it was 7072. The corresponding figures for the Children's Hospital, Sheffield, were similar; that for 1947 was 2139; that for 1959 was 6728. The figure for the Booth Hall Hospital, Manchester, in 1953 was 2931, in 1959 it was 5227.

DISCUSSION

Our figures have conclusively shown the inaccuracy of the oft-repeated statement that the work of children's hospitals in this country is declining. Our figures show, on the contrary, that the pressure on children's beds and on outpatient clinics in children's hospitals has considerably increased in the past ten or twenty years. In almost all, the increased turnover has been achieved without an increase in the number of beds, and often with a smaller number of beds, wards having been closed for long periods because of a shortage of nurses or structural alterations. Admissions have risen despite increased efforts by practitioners, on psychological grounds, to avoid admitting children.

We were unable to obtain figures from most of the hospitals to show the mean duration of stay. Those figures which we did obtain were impressive. For instance:

At the Jenny Lind Hospital, Norwich, the mean duration of stay was less than 7 days in each of the last four years of the period. At the Derbyshire Children's Hospital it was less than 8 days for each of the last four years. In 1959 the mean duration of stay at the Children's Hospital, Sheffield, was 9·7 days. 36% were discharged in less than 3 days, and 61% within 7 days of admission. In Bristol the mean duration of stay fell from 20·1 in 1949 to 12·9 in 1958.

Spence and Taylor (1954) remarked that hospital beds are used more effectively, with higher turnover in numbers, when children's wards are grouped together into children's departments or children's hospitals; and Taylor and Davison (1959) wrote that the length of stay in hospital rises considerably when the children are nursed in a unit without pædiatric supervision. It is obvious that the reduction of stay in hospital by the more efficient use of beds has important financial implications.

The figures which we have supplied do not give a complete picture of the increased work done by children's hospitals in recent years. Several consultants wrote to me that the number of infants admitted relative to older children was rising, and that this means much more work for the staff. This certainly corresponds to our experience in Sheffield. In addition, the ever-increasing complexity of special investigations and of surgical procedures places an increasing load on the medical and nursing staff. The increased turnover, with the reduced mean duration of stay, inevitably increases the work of the nurses.

Our figures have also shown that the volume of outpatient consultative work and of casualty work has considerably increased during the period.

In our opinion the work of children's hospitals and large children's units in general hospitals should increase still more over years to come. They certainly will do so, if they take the children they should take, and if they are given the beds which they need. There are still far too many children being nursed in small units without pædiatric supervision. In any case, the more children are concentrated in large units, the more efficient is their care likely to be.

Many children are still nursed in infectious-disease hospitals, many of which have no pædiatric consultant staff. The idea that children with certain infections should be nursed in one sort of hospital, while others with equally infectious conditions should be nursed in children's hospitals or children's units of adult hospitals, is surely an anachronism. Each children's hospital and large children's unit should have its own isolation unit, so that it can treat all infectious diseases which need hospital treatment.

Many children are nursed in adult wards. The Division for Architectural Studies of the Nuffield Foundation showed that in fourteen hospital groups in different parts of the country, of 17,830 children in hospital at one time, 5073 were in adult wards. It is now well recognised that this practice is thoroughly undesirable.

Taylor and Davison (1959), writing about the greater efficiency of large pædiatric units, as compared with small ones, stated that the fact that each year in England and Wales nearly 2000 infants die from acute respiratory disease, many at home, suggests that some who need admission are still not admitted: and that the fact that 200 children die each year in England and Wales from appendicectomy and intussusception, when the mortality from these in experienced hospitals is extremely small, suggests that some are not treated under optimal conditions. They advocate, as many others have, that beds in adult wards and in small isolated children's wards should no longer be used by children. The children should instead be housed in large pædiatric units of general hospitals or in children's hospitals. In discussing the argument that concentration of children in large units would make visiting difficult, they rightly comment that ease of visiting does not compensate for long illness, residual disease, or a dead child.

SUMMARY

We have investigated the number of admissions of children and of new outpatient consultations in twenty-two children's hospitals outside London from 1947 to 1959.

In almost all hospitals there has been a considerable increase in the number of admissions and new outpatients seen during the period. In the nineteen hospitals with full data available, there was an overall increase of nearly 18,000 admissions between 1950 and 1959. In seventeen children's hospitals with complete data, the increase of new outpatients between 1952 and 1959 was over 12,000. There was a considerable increase in new casualty attendances.

Our figures show conclusively that the work done by children's hospitals has increased considerably since 1947–50.

Our thanks are due to the following consultant pædiatricians and to the secretaries of the hospitals for providing the information for this paper: Dr. R. A. Shanks, Glasgow; Prof. J. Craig, Aberdeen; Prof. R. W. B. Ellis, Edinburgh; Dr. G. Davison, Prof. S. D. M. Court, Newcastle; Dr. J. B. Heycock, Sunderland; Dr. J. J. Tillie, Stockton; Prof. J. Hey, Liverpool; Prof. W. Gaisford, Manchester; Dr. M. W. Arthurton, Bradford; Dr. B. M. Laurance, Derby; Dr. M. G. Philpott, Hull; Prof. D. V. Hubble, Birmingham; Dr. A. P. Page, Nottingham; Dr. J. F. P. Quinton, Norwich; Dr. Beryl Corner, Bristol; Dr. J. A. J. Williamson, Southampton; Dr. T. Mann, Brighton.

REFERENCES

Gairdner, D. (1956) *Proc. R. Soc. Med.* **490**, 974.
Spence, J., Taylor, M. D. (1954) *Lancet*, i, 719.
Taylor, M., Davison, G. (1959) *ibid.* ii, 453.

Special Articles

AUTOMATION IN CLINICAL BIOCHEMISTRY

MUCH of the work performed in hospital laboratories requires attention to individual detail and an eye for the unexpected. Some of the routine operations, however, are well suited to mechanical processing: the ' Histokine ' has cut delays and drudgery in the histology department, and automatic red-cell counters are appearing in hæmatology laboratories. Chemical analysis by automatic means is well known in industry, and its adaptation to hospital conditions could be expected. The simplest step in automation is the mechanical delivery of measured volumes of liquid, and most visitors to laboratories have seen the home-made automatic pipettes based on syringes or gin-dispensers which have served as prototypes for a number of commercial models of variable predictability. More recently, complete mechanical procedures for biochemical analysis have been devised by Skeggs,[1] and a commercially made version of his apparatus has been in service for up to two years in several hospitals. The prototype of a similar instrument has since been described by Jonnard.[2]

The appearance of such a machine breaks new ground, even though its main, and surprising, feature is an adherence to traditional methods of analysis. As its main new departure the method eliminates measurements of volume (except in the preparation of reagents), replacing it by a continuous process in parallel channels, in which streams of reagents and blood travel at identical speeds and react with each other by diffusing across a semi-permeable membrane separating the channels. Specimens are loaded by hand and are drawn through the apparatus, which consists of a dialyser, a heating-bath for some of the analyses, and a continuous-recording photoelectric colorimeter. The method of analysis is always colorimetric, and the results on the chart are worked out by the operator. The machine is therefore a straightforward mechanised version of what is done by hand in biochemistry departments.

Though this automatic analyser may only be the first of its kind, its existence is bound to affect hospital laboratories and even the development of clinical biochemistry as a subject. Its main effects are likely to be these:

1. Since automatic operations are more easily controlled than manual ones, methods requiring strictly standardised conditions can now be introduced into routine practice; the diacetyl-monoxime method of estimating blood-urea,[3] which tends to be erratic when carried out by hand, now serves as a satisfactory automatic procedure. The way in which a major piece of equipment influences thinking is of course not without its dangers, and biochemists may come to think of new methods in terms of the automatic analyser they already have, even where a colorimetric method would not otherwise be the method of choice.

2. Automatic methods give more accurate as well as more reliable results, the latter being the more important. Though experimental accuracy need not be refined much beyond clinical requirements, manual methods sometimes fall short even of this standard; but the occasional stray results are far more disturbing, especially since clinical staff cannot be expected always to bear in mind that a biochemical result represents a probability within two standard deviations. Stray results can often be traced to the distracting conditions of a busy hospital laboratory, to which the machine is not sensitive.

3. Most laboratories will want to keep the machine on a tight schedule, switching from one method to another at set times of the day. It will not be convenient to stop a run to deal with an urgent request out of turn, or to start the machine in an emergency at night. To retain the present manual methods would defeat some of the objects of automatic analysis; the need is for a set of emergency procedures, accurate enough for immediate purposes. These new bedside methods are likely to be of the commercial tablet or matchstick type. The blood sample can then be saved, and the exact result obtained at leisure.

4. The fifteen mechanical methods available at present account for the bulk of routine work. Since running the machine requires only unskilled machine-minding with some expert supervision, automation will release skilled workers to introduce estimations now restricted to specialist centres. It may ultimately affect laboratory staffing, accentuate existing differences between biochemical technicians training in small laboratories and those in large mechanised departments, and necessitate radical changes in their examination syllabus.

5. Economic consequences are also to be expected. The initial cost of the apparatus, the turnover required for saving on running costs, and the increased reserve capacity of the machine (the marginal cost of adding more specimens to a batch is slight, whereas a technician's efficiency will decline beyond an optimal batch size[4]) mean that departments installing automatic analysers already have large work loads or expect to have them. Automation will make these large laboratories more efficient and will accentuate the difference between large and small centres; it will be useless to plan small biochemistry laboratories in the knowledge of technical developments, and then to argue that automation in these small laboratories is not economically feasible. A number of similar points arise: for instance it will be wasteful to keep a technician stationed in the diabetic clinic to do blood-sugar tests manually if better results can be got more quickly, so that the relative siting of laboratories and outpatient departments will require renewed attention when our new hospitals are planned.

A. L. TÁRNOKY.

1. Skeggs, L. T., Jr. *Amer. J. clin. Path.* 1957, **28**, 311.
2. Jonnard, R. *Ann. N.Y. Acad. Sci.* 1960, **87**, 669.
3. Fearon, W. R. *Biochem. J.* 1939, **33**, 902.
4. Verschure, J. C. M. *Scand. J. clin. Lab. Invest.* 1957, **10**, suppl. 31, p. 317.

POLIOMYELITIS VACCINES

THE Minister of Health, in answer to a question in the House of Commons on April 12, indicated that inactivated poliomyelitis vaccine would, for the present, remain the type to be provided for the official vaccination scheme. This course was advised by the joint subcommittee of the English and Scottish Medical Advisory Committees which has throughout advised the Health Ministers. The subcommittee has also advised that fourth doses should be offered to children of primary-school age—that is, from the age of five up to eleven years—who have already had three doses.

A British attenuated vaccine for administration by mouth has been produced, but the subcommittee does not advise its use in the normal vaccination scheme yet. Further studies of the ability of this vaccine to colonise the intestine and uniformly lead to the production of antibodies are in progress. There are, however, circumstances in which the ability which attenuated virus strains are believed to possess, to colonise the intestine and so block the spread of wild virus in the community might give advantages in controlling a developing local outbreak. It is not certain that such an effect could be obtained under British conditions with a population already well immunised. The prospect of complete success in this respect depends on feeding live vaccine to the bulk of the local population within a matter of days—a formidable undertaking requiring elaborate organisation and a ready public response.

The subcommittee advised that there should be a reserve of live vaccine. This has been arranged. It will be held against the possibility of mass use being thought desirable and practicable in an area with a developing local prevalence.

The vaccine is composed of the Sabin strains of attenuated virus. It is stored in concentrated form and would be diluted in buffered syrup for oral administration. Vaccine of a virus type different from that of the wild virus causing disease in the area would be chosen. Distribution locally would have to be determined by the circumstances of the area and the outbreak. Medical Officers of Health have been informed of the position.

Parliament

THE BUDGET

INTRODUCING his first Budget on April 17, Mr. SELWYN LLOYD, the Chancellor of the Exchequer, said that one of the problems he faced was the continuing growth in public expenditure. Most people no longer held the view imputed to the 19th century that all public expenditure was bad and all private expenditure good. Nowadays, all political parties were committed to a high and rising level of expenditure on education, public health, and other public services. But though this was accepted, public expenditure must not be allowed to outrun the prospective growth of our resources. It should not take too much of our resources from other forms of economic activity where growth was most likely to come. We must, therefore, get the priorities as nearly right as we could, both within the public sector and between the public and the private sectors. This called for new methods. We needed increasingly to look at all public expenditure together instead of piecemeal, and to look at it for a period of years in relation to prospective resources. He had recently set in hand a study of the whole problem of public expenditure in relation to the prospective future growth of our resources for a period of five years ahead, with the object of seeing how we could best keep public expenditure in future years in proper relationship to the growth of our national product. He believed that there were savings to be made by so-called administrative economies, and that if those, at all levels, who have charge of the spending of public money would bring to the task the same prudence they apply to their own financial affairs the results would be worth while.

Mr. Lloyd's fiscal proposals for 1961–62 include a modest increase in the tax allowance for National Insurance contributions (from £15 to £18) in recognition of the changes which the graduated National Insurance scheme will bring. In view of the higher National Insurance retirement pensions now payable he also proposed to increase by £20 the income limit for the dependent-relative allowance. The increase in motor-vehicle duties excludes ambulance and invalid carriages which are at present exempt.

More substantial changes deal with surtax. Earned income allowances will become deductible in computing income for surtax, and the tax will begin at £4000 instead of £2000. Taken together these two proposals mean that surtax will not be payable on earned income until it reaches £5000 (or more for taxpayers with children), but the new rates will not affect the amounts due in January, 1962, on income earned during 1960–61.

Justifying his surtax proposals, Mr. Lloyd said that in the modern world the work of the manager, the scientist, the technologist was of increasing importance to the community. He wished to ensure that surtax did not act as a disincentive to those who had positions of responsibility in our industries and elsewhere in our national life.

As part of the Budget, Mr. Lloyd also asks for power to introduce during the year a pay-roll tax of up to 4*s*. per employee per week. This would act as an incentive to economy in the use of man-power and to investment in labour-saving equipment. As a temporary expedient he would collect this surcharge by attaching it to the employer's share of the National Insurance stamp. But he recognised the risk of confusion between this surcharge and the contribution, which might undermine the contributory principle on which National Insurance was based, and he would continue to examine other methods of levying it.

Mr. HUGH GAITSKELL, opening the debate as leader of the Opposition, suggested that the proposed pay-roll tax would fall heavily on concerns which use a large amount of labour; which, though he did not mention it, would seem to include the National Health Service. He did, however, mention the service in his criticism of the surtax adjustments. The Chancellor, Mr. Gaitskell pointed out, had taken in a full year about £60 million off surtax, which was very close to the amount he had imposed in the increased health service charges and contributions. He continued, " What happens is that a man on £10 a week is to pay 10*d*. a week more in contributions and is to pay more when he goes to the doctor for his prescription, and the man earning £2000–£5000 a year is to be substantially better off ".

Criminal Justice Bill

AT the report stage of this Bill in the House of Commons on April 11, Sir THOMAS MOORE sought to introduce a new clause giving the courts power to pass a sentence of corporal punishment on young male offenders convicted of a second (or subsequent) crime of violence. Mr. R. A. BUTLER, the Home Secretary, resisted the proposal. Though he agreed that there was anxiety in the country about the present state of crime, he did not believe that corporal punishment was the right remedy. The whole object of the Bill was to provide alternative methods of dealing with young offenders. One of the most important would be detention centres, where, he assured the House, the regime was strict. He admitted that till recently progress in building these centres had been too slow, and when the Bill was first introduced there were only a few. There were now 7, of which 3 had been opened since the second reading. 6 more centres were planned, 2 of which would be opened this year. In all there would be 13, which was 1 more than originally promised.

Sir REGINALD MANNINGHAM-BULLER, the Attorney-General, said that, as the rejection of the clause was a Government decision, there could be no free vote; but 67 Conservative members voted for it. With the help of Opposition members it was, however, defeated by 259 to 67 votes after a debate of over five hours.

Mr. J. E. MACCOLL moved the insertion of a new clause raising the age-limit for the death penalty from 18 to 21. But Mr. BUTLER said that the Government were unable to accept the clause because they felt that it was too soon to draw conclusions about the result of the Homicide Act of 1957 and because of the great increase in crimes of violence committed by people aged between 17 and 21. To raise the age-limit now might give some young people the idea that capital murder was not a heinous and terrible crime. The clause was rejected by 229 votes to 144.

Mr. Butler moved the deletion of an amendment made in committee providing that children under 16 should not be sent to borstals until adequate remand centres were available. He sympathised with the motive behind the amendment, which was to prevent children being sent to prison on remand. But as it stood now, the Bill would prevent magistrates from sending a child to a borstal when they considered that the most suitable form of training, and he thought that issue was more important. He agreed that owing to the big drive for building prisons and detention centres too little progress had

been made with remand centres. But a complete programme had now been drawn up. They were proceeding with Risley in the North West of England as an all-purpose adult and juvenile centre, but then, in the first place, centres for young offenders only would be provided. The first would be opened about next July at Ashford to serve the London area. Sites for a further 7 were in view. The programme could not be completed under three years but it would cover the whole country.

Miss ALICE BACON, while welcoming news of this building programme, pointed out that not one centre had yet been built. If the amendment was removed from the Bill, 15-year-olds might have to spend their remand period sleeping three in a prison cell. Mr. BUTLER said that it was repugnant that there had to be any question of remanding young people to prison, and he gave the House a pledge that while this had to continue segregation should be real and effective. The House agreed by 205 votes to 132 to remove the amendment made in committee.

Road Traffic Bill

SPEAKING in the debate on the second reading of this Bill [1] in the House of Lords on April 13, Lord TAYLOR discussed technical aspects of the blood, breath, and urine tests proposed for use in cases of alleged drunkenness. He believed that they were well worth doing in the interests of both justice and road safety, provided that they were properly done. The tests and equipment must be standardised. Those who did the tests must be trained. The results must be expressed in a standard way. If these precautions were taken, the courts would find the tests of great value and public confidence in their validity would soon be established. He thought that clinical examinations should be retained, recognising their grave limitations and hopeless imprecision when it came to precise definitions of drunkenness. Their value was only to exclude other conditions—such as head injury or hypoglycæmia—which might cause confusion. Police often had difficulty in finding a doctor to make these examinations, and Lord Taylor suggested that in every area the police should pay a retaining fee to a doctor who would undertake this unpleasant work regularly.

Dangerous Homes

ON April 12, in the House of Lords, Lord AUCKLAND pointed out that the number of accidents in the modern home, with all its electrical equipment, was still higher than the number of accidents on the road. Compared with other sources of accidents, such as factories and mines, the home was unsupervised and its fatalities unpublished. 80% of these accidents befell children under five and adults over sixty-five. Indeed for these small children accidents in the home were the third largest cause of death. Many of the accidents were burns and scalds. Unguarded fires and inflammable night clothes were too often the cause, but he also mentioned polyethylthene bags, fireworks, and firearms. Lord CROOK spoke of "beautifully coloured dangerous drugs" and deplored the over-glamourisation of the medicine cupboard.

Lord AMULREE said that when people grew old they were more inclined to fall, but much could be done to cut down the number of falls. Stairs, steps, electric wires, gas taps should all be safeguarded. Lord TAYLOR added to the list of hazards for old people collisions with household objects, glass, whether in windows or bottles, unlaced shoes or worn slippers, faulty equipment, such as the old blunt knife, the rickety chair, the saucepan with the loose handle. On the whole, disregarding age, he thought that accidents tended to occur among people who were socially and domestically incompetent. In his view health visitors were the key people who could teach domestic efficiency in the home. The Government should stimulate their recruitment and train them in the prevention of accidents.

1. See *Lancet*, April 1, 1961, p. 716.

QUESTION TIME

Transfer of Prisoners To Hospital

Under section 72 of the Mental Health Act 10 people with psychopathic disorders have been transferred from prisons, borstals, or approved schools to hospitals. 4 are detained in Broadmoor Hospital, 4 in Rampton Hospital, 1 in Stanley Royd Hospital, and 1 in Harperbury Hospital.

Public Health

Less Strontium 90 in Milk

THE quantity of strontium 90 (^{90}Sr) in milk produced in the United Kingdom during the first half of 1960 is given in the fourth report [1] of the Agricultural Research Council's series dealing with fallout contamination of human diet in this country. During the late spring and early summer cattle were grazing for the first time on herbage which had grown after the rate of fallout had been relatively low for several months; on average milk produced during the latter part of May and June contained 48% of the ^{90}Sr observed twelve months earlier. The mean for the twelve months ending June, 1960 was 10·3 $\mu\mu$C per litre or 8·4 $\mu\mu$C per g. of calcium—about 15% less than the corresponding figure at the end of 1959. Samples taken after June indicate that the levels in milk continued to be much below those observed at the same time in 1959.

In "special areas" where high rainfall and local agricultural conditions lead to higher levels in milk, no consistent downward trend in the twelve-month mean values was apparent by the end of June, but in May and June the results for half of the areas were less than two-thirds of those twelve months previously. The highest value for an area from which a continuous supply of milk has been available was 68·3 $\mu\mu$C per litre or 60·5 $\mu\mu$C per g. of calcium. Results in 1958 showed that the effective delay period in the transfer of ^{90}Sr from rain to milk during the spring and early summer is longer in the special areas than elsewhere. Thus it is not surprising that the decreasing rate of fallout has not affected the twelve-month mean values as rapidly as in the countrywide survey.

The new results justify the expectation that the mean level in the total mixed diet of the population, as well as in milk, will be appreciably lower for 1960 than for 1959.

Protection against Unsealed Sources of Radiation

THE Ionising Radiations (Sealed Sources) Regulations have already been issued by the Ministry of Labour as a statutory draft.[2] A complementary draft code [3] dealing with the use of unsealed radioactive sources in industry and in nuclear reactors was published as a preliminary draft on April 14.

The standards of shielding and the permissible doses of radiation are the same as those laid down for sealed sources, but the regulations are more complex and detailed because of the greater hazards of unsealed sources. An important difference between the regulations is that no-one under 18 may work with unsealed sources. The requirements for medical examination, before and during employment, are the same as those for workers with sealed sources.

The new regulations will supersede the Factories (Luminising) Special Regulations, 1947, and forbid the use of brushes for handling radioactive substances. No instrument or apparatus operated by the mouth is allowed.

A schedule to the regulations lays down the method of calculating the amount in units of the different radionuclides. The unit may be less than the millicurie-content of the substance and depends upon the group, of which there are four, to which the radionuclide is assigned. A second schedule specifies the maximum permissible level of contamination.

Observations on these regulations must be sent to the Minister by July 31, 1961. The date on which the regulations come into force has not yet been fixed.

1. Agricultural Research Council Radiobiological Laboratory Report no. 4. H.M. Stationery Office. Pp. 81. 5*s*.
2. See *Lancet*, April 7, 1961, p. 781.
3. Unsealed Radioactive Substances Regulations. Pp. 28. 1*s*. 3*d*. H.M. Stationery Office.

In England Now

A Running Commentary by Peripatetic Correspondents

LIKE all other householders in Great Britain, I have been studying my homework for next weekend. But I find my attention distracted from my own Census problems by the tantalising glimpses offered me by the Registrar General of the families he has chosen as "examples of completed schedules". The Whites are fairly straightforward—father and mother in their 50s and their daughter Anne, aged 20. But even they have a mysterious Irish visitor. Is Colin O'Leary, aged 40, a younger brother of Mrs. White or has he, despite his married status, come to see Miss White? The Spencers also have visitors. Paul Le Sage, Mrs. Spencer's son by her first marriage, has come over from Paris to confuse our Census, and Francis Lee, though he only lives at Clapham, has insisted on staying the night. Still the Spencers are lucky, for they seem to have domestic help in the form of the twice-widowed Mrs. Emma Clark. I bet they had some difficulty in establishing her age at 54 years and 2 months. The Foster household worries me even more: Mrs. Foster is the acting head, but where is Mr. Foster—away on business or in hospital? His absence is all the more regrettable because young Robert Foster and his wife Sylvia have come to stay with their baby, who was born in Germany less than a month ago. Was it wise to travel with such a young baby? But perhaps they have come over for the christening, and if so why has baby Foster's name not been settled? But perhaps Robert has just finished his National Service, and Mr. Foster, senior, is absent because quarters are cramped now that the young people have returned. If so, will the boarders Ellis and Janet Hughes, aged 30 and 29, now have to find other lodgings?

It's all very unsatisfactory, and I can't help wondering whether Dr. Dale has received *his* form safely.

* * *

To hear some people talk you'd think the psychosomatic approach was new. But those old clinicians had it all—except the jargon. Thirty years ago in the wards we learned the pure doctrine of stress, the effect of the environment, the relationship of "heredity and strain". Of course there was not much biochemistry around the hospital bed. There was more "basic science" at that time in the repulsive world of public health, where you might meet nitrites in water-supplies and arsenic in beer. In those laboratories it was difficult to perceive the patient. Now the hygienists have loosened their attention from the titrations and are busy with mental health. While the frenzy of laboratory techniques has moved to the wards—where it becomes increasingly difficult to perceive the patient.

* * *

The six-year-old patient was on the table for eight hours: sternum split; both groins opened. Three cannulæ penetrated the heart, apart from endless intrusions of one kind or another elsewhere. Œsophageal temperature was reduced to 10°C, and he lay before us, dead to any clinical test, for half an hour. Two surgeons, two anæsthetists, a physician in charge of the apparatus, the usual theatre staff, a small army of hæmatologists, and some technicians were in attendance.

Two days later I visited the boy in his ward. "Hullo, old chap!" I said, "I wanted to see how you were getting on: I was at your operation." "You were?" He cocked a suspicious eye in my direction. "That operation," he continued; "they pricked my finger: it still hurts!"

* * *

Anyone who's listened to a tape-recording of their friends' conversation knows that in everyday life we don't talk with incisive Shavian purposefulness. Even so, I was a bit surprised the other evening when I came home to find my wife flat out after throwing a tea-party at which the guest of honour had been a fine old lady who is so deaf that her only means of learning what others are chattering about is the written word. This is what I found on a pad:

I didn't know they were called primroses. They are in the garden next door.
We came in 1951.
Have you been in an aeroplane?
Have you any help now?
No, but I know some friends who enjoyed it.
We go to N. Wales for our holidays.
David wants to go into insurance.
They have tried water softeners, but Mrs. Watson came out in spots and is not keen on it.
Up the road at 61.
What a long time you have lived in London Road.
Skiing. Joanna has hurt her leg.
Yes, a young boy was driving. He was an L.
There are so many houses being built round here.
Not long journeys. From India to Ceylon.
9 years.
A secretary. She is going to St. Christopher's. Mrs. Smith has 4 children, all very clever.
They are talking about snakes.
Have you played golf?
Yes, Ross.
Budgerigars very expensive.
Foxes.
Twenty hens lost last year.
They are beautiful.
Not very much.
Do you know our vicar?
Into the country.

Other things being equal, I couldn't agree more.

* * *

The contrast of the powder-room and rest-room of the business establishment which I had just left and the barren, end-of-war food-office appearance of the room in the Civil Service department to which I was called was astonishing. A wooden bench and ex-W.D. wooden table served in the women's rest-room for tea-breaks. The girl who had fainted was stated to have been unwell for days, and as there were no facilities for examination, or elementary privacy, I suggested they get a taxi and take her home where she could be seen by her own doctor. However, as she lived out of town, I suggested the taxi could take her to the casualty department of the nearest hospital and I would telephone the casualty officer. The supervisor had demurred about calling a taxi and as I left I heard him calling an ambulance. I turned and remonstrated, pointing out the unnecessary trouble all round that his action would cause, as well as the needless additional expense. His reply was abrupt. "There's no petty cash in this Civil Service department. If I paid for the taxi, there'd be a helluvan-inquest."

* * *

My post had a smell of the sea this morning. Though my office is 100 miles from the nearest coast and about double that distance from a port of any size, the Ministry of Health informed me that should there be, by any chance, in my Midland county a shipbuilding yard, the regulations about ambulances had been revised.

* * *

INTIMATIONS OF IMMORTALITY 1961

Dribble, dribble, Little Star—
So we can know just how you are;
Is your saliva thick or clear
Up there in the Ionosphere?

How we exult to hear you bark
Up there in your celestial ark!
It's only a preconditioned reflex, true,
But Pavlov would be proud of you.

To think it was *us* who sent you up,
Alone in your triumph, intrepid pup!
But what is this? A hollow laugh
Recorded by the encephalograph?

Starlet, Starlet, don't complain,
We'll very soon have you down again—
Think of the glory! And if we fail,
We can study the last few waggings of your tail.

Letters to the Editor

NEEDS AND BEDS

SIR,—In their encouraging paper of April 1, Dr. Tooth and Miss Brooke have made a forthright prediction. They say that discharge and death of long-stay patients—that is, those who had already spent 2 years in mental hospitals by Dec. 31, 1954—reduced this particular population by 28% for males and 32% for females in the following five years. On this basis none of them, they say, would remain in hospital by about 1970. This forecast has been inaccurately repeated in a recent Ministry of Health circular [1] in which there seems to be some confusion on whether these estimates relate to 16 years from now or to 16 years from 1954.

For some reason Dr. Tooth and Miss Brooke have assumed that the decline in the number of long-stay patients will be linear, although a rearrangement of their table III shows that this is improbable.

Long-stay patients in hospital on Dec. 31, 1954		112,113
Deaths and discharges	1955	8163
" " "	1956	7432
" " "	1957	6608
" " "	1958	6246
" " "	1959	5953
Remaining on Dec. 31, 1959		77,711

This looks more like a curve to me. Where the end-point of the curve would be is arguable, but it is certainly farther away than 1970. Common sense gives the same answer. Any doctor working in a mental hospital can, I am sure, think of many patients admitted before 1953 who (short of major changes in policy and much more effective new treatments) are very unlikely to die or be discharged in the next 10 years.

A different guess, curiously enough relating to an almost similar group of patients—i.e., those admitted before 1954—was made recently.[2] Although the patients concerned were all women and confined to one hospital, the forecast could probably apply to the general mental hospital population; then, of the 77,700 patients who on Dec. 31, 1959, had been in hospital continuously for 7 years or more, perhaps 25,000 would still be there in 1970, 13,000 in 1975, and 6000 in 1980—instead of none, as Dr. Tooth and Miss Brooke have forecast. The forecast in the Ministry circular that " in 16 years or a little more " only about 80,000 beds will be needed for mental illness may be an underestimate of from 10,000 to 25,000, depending on whether the 16 years date from now or from 1954.

The news from mental hospitals in the past five years has been very good. It is a pity to make it seem even better than it is.

Bexley Hospital,
Bexley, Kent. ALAN NORTON.

SIR,—The admirable paper by Dr. Mackintosh, Professor McKeown, and Dr. Garratt (April 15) emphasises the difficulty of this subject, especially the concept of " clinical need ". Every clinician knows that a certain number of medical beds are occupied by unnecessary admissions. Attempts to measure this number, however, yield markedly different results.

In a series quoted in this paper, a group of Birmingham physicians, assessing their own cases, found only 3·8% of unnecessary admissions, but an independent observer, reviewing the same group, put the figure at 22·2%. Happily, the two sides then got together and reached a useful compromise of 13·3%.

In Barrow, our figures for admission per head of population, are a little less than the national average. Presumably the diseases in Barrow do not differ greatly from those in Birmingham, yet Forsyth and Logan [1] considered a quarter of the male and two-fifths of the female cases to have been admitted unnecessarily. In this survey, contrary to the statement in the paper of Mackintosh et al., Dr. Logan was the sole arbiter of " clinical need ". In this connection the opinions of the clinicians in charge of the cases were not sought and, when Dr. Logan's results eventually appeared, they were surprising. What is the explanation for these widely discrepant results? I suggest that it lies in three main directions:

Firstly, no-one has succeeded in laying down satisfactory criteria by which an independent observer can recognise and test for " clinical need ". In these circumstances, the decision on whether a case has been admitted to hospital because of " clinical need " or not depends upon a purely subjective assessment. Figures based upon such assessments are still matters of opinion, even when expressed as percentages to the first decimal place.

Secondly, no worker in this field has yet taken adequate steps to eliminate observational bias. That such bias operates seems to be quite self-evident from the data presented in this article.

Finally, although most of the cases in a medical ward are acute admissions, assessments of " clinical need " appear, in general, to have been made retrospectively.

It is only too easy to be wise after the event and miss what has been an urgent clinical situation demanding admission. It may well be that there are no practical means of meeting these criticisms of method; but until they are met, figures based upon estimated " clinical need " will, I submit, merit little confidence, at least in a scientific sense.

North Lonsdale Hospital,
Barrow-in-Furness. A. P. B. WAIND.

TRANSIENT AND INTERMITTENT SYSTOLIC MURMURS IN NEWBORN INFANTS

SIR,—Dr. Benson, Dr. Bonham-Carter, and Dr. Smellie (March 25) are to be congratulated on the size of their survey (11,855 babies examined in 10 years); and it is only unfortunate that what they call " considerable observer error " should have resulted in their reporting such a low incidence of murmurs as 0·94%.

In a previous study at Southmead Hospital, Bristol,[2] it was clearly shown that if anything approaching the true incidence of these neonatal murmurs was to be recorded, then a single experienced observer should examine each infant regularly, if possible daily. Two examinations on the 1st and 9th days, carried out by recently qualified housemen, would not to my mind suffice: had the infants in the Bristol series been examined so infrequently the overall incidence of 38% would have been reduced to 10%. Frequent examination is seen to be even more essential when we consider the transient nature of the murmurs in many cases: 47% of the murmurs in the Bristol babies, though repeatedly listened for, were heard on one occasion only during the neonatal period. The 50 infants in the Bristol series were examined, in all, 585 times.

This study at University College Hospital, London, appears to have performed a useful function in discovering cases of congenital heart-disease (39% of 111 newborn babies with murmurs), but does not tell us the true incidence of systolic murmurs in the neonate—present much more often, I believe, than is generally realised, and which, in my view, are infrequently due to appreciable malformation of the heart.

South Shields,
County Durham. R. D. G. CREERY.

THE TIGHT BRAIN

SIR,—I have read Dr. Marshall's article (April 8) and am in complete agreement with its practical implications. For a number of years I have realised that the best results can be obtained only by a combination of techniques.

For supratentorial lesions I favour controlled respiration, which is simple, can be used with hypothermia or hypotensive techniques, and gives the best operating conditions.

1. HM (61) 25, para. 3.
2. Norton, A. *Brit. med. J.* Feb. 25, 1961, p. 528.

1. Forsyth, G., Logan, R. F. L. The Demand for Medical Care. London, 1960.
2. Creery, R. D. G. *Ulster med. J.* 1953, **22**, 73.

With controlled respiration, if the blood-pressure is above 150 mm. Hg, it should be lowered to approximately 110 (but never below 100, except in hypothermia) to improve operating conditions. This applies even with hypothermia or with hypertonic infusions.

In my experience induced hypothermia to 30–32° C often raises the blood-pressure, has little effect on brain bulk, and is only valuable in difficult cases or where extreme hypotension is required. This raised blood-pressure must be lowered to about 110, otherwise the operation will become difficult.

Hypertonic solutions (particularly of urea) if infused too rapidly invariably raise the blood-pressure and make bleeding very troublesome. Reduction to 110 is again indicated.

To facilitate the neurosurgeon's task, is there any contraindication to the use of intravenous urea, administered slowly under strict supervision on the night before operation, or as a slow drip while the patient is cooling when hypothermia is induced?

Morriston Hospital,
Swansea,
Glamorgan. J. M. LEWIS.

EFFECTS OF CHLORDIAZEPOXIDE

SIR,—The letter from Dr. Currie (April 1) describing his results with chlordiazepoxide in rheumatic patients is very interesting. I have not found the peculiar hypnotic effects that he describes, but have been giving a dose averaging 30 mg. per day rather than the 200 mg. that he gives. I feel, however, that his letter paints a rather gloomy picture of its value in rheumatic disorders.

I have now used this compound in almost 100 patients with musculoskeletal disorders. Although I would agree with Dr. Currie that this compound has no direct antirheumatic or analgesic effect, particularly in rheumatoid arthritis, nevertheless in many patients pain has been strikingly relieved, and they have been more mobile. This has been most noticeable in patients with pronounced muscle spasm. In these patients the compound appears to be valuable therapeutically.

London, W.1. L. B. BLOMFIELD.

SKELETAL FLUOROSIS

SIR,—In spite of intensive study of Dr. Alcock's letter (March 11), I have been unable to find any statement justifying the construction put on it by Dr. Dobbs in his first paragraph (April 1).

Again, *unless* skeletal fluorosis is the only recognisable effect upon adults of a high fluoride intake, why is it pointless to ask doctors in study areas "to report on any abnormal morbidity which they thought might be attributed to fluoridation of water supplies". Dr. Dobbs cannot have it both ways.

Either there is no effect apart from skeletal fluorosis, in which case no medical investigations are needed; or there is, or conceivably might be, in which case practitioners who have unique opportunities to observe patients in low as well as in high fluoride areas might make a vital contribution. Their findings, if suspicious, could then be intensively investigated. In fact, it was a parallel observation about the state of the teeth in high and low fluoride areas which brought to light the knowledge of the beneficial effects of an optimum level of fluorides in the control of dental caries.

As a medical officer of health, I cannot recall any statistical evidence for "an appalling increase in chronic diseases" either locally or nationally—other than that due to the ever-increasing proportion of the population surviving into later life. In other words, the more old people, the more chronic disease there is likely to be; and every year there are more old people.

To bring the amount of a *normal* constituent of water up to a level found naturally in many supplies which have been drunk with impunity for generations cannot be regarded as "pollution" in any sense of the word.

Dr. Dobbs' assertion that the approval by various scientific bodies of fluoridation, "reflects primarily the successful activities of their more politician-like members", is a very serious allegation. It implies that the various bodies throughout the world which have examined the relevant issues are not impartial; but what have they to gain from their bias?

Public Health Department,
St. Faith's and Aylsham
Rural District Council,
Norwich, Norfolk. IRENE B. M. GREEN.

MOUTH-TO-MOUTH ARTIFICIAL RESPIRATION

SIR,—Lord Taylor's recent handbook, *First Aid in the Factory*, is commendable for its exposure of many of the traditional fallacies in first-aid teaching. I was thus all the more shocked that, although the author conceded that the oral method of artificial respiration as first practised by Elisha [1] was "undoubtedly very effective", he should condemn its teaching as "impracticable for the present".[2] His case rested upon the argument that "it is very hard to teach to first aiders", and "the only practical teaching method is to use an expensive human dummy". He then proceeds, at length, to urge proficiency in the Holger-Nielsen manual method. I suggest that Lord Taylor is not only conservative in adopting this attitude but also seriously in error on points of fact.

The medical committee of the International Convention on Life-Saving Techniques [3] declared that "expired air artificial respiration is recommended as the best universally applicable field type of artificial respiration". There is abundant evidence for the view that it is easily taught.[4 5] In experiments with Royal Naval personnel, Cox et al.[6] found the method "easy to teach to untrained subjects" and there was "certainly no general fatigue". This was despite the use of an accessory airway to overcome æsthetic objections. Indeed, the technique has been carried out by previously untrained operators for periods of up to 115 minutes, and Danish workers have shown that children of 12 years and upwards are able to perform the method successfully on fully grown adult anæsthetised and paralysed subjects.[7] The fire department of the City of New York has found that it is easily applied by laymen in the field.[8]

Lord Taylor's second criticism—that an expensive human dummy is required in training—is unsound. Even if cost is to be assessed solely in absolute terms, the new Siebe-Gorman model is scarcely "expensive" at under £10. The admittedly costlier full-size Scandinavian models at up to £30 are not more expensive than a real skeleton, or indeed a single course of elementary lectures to a first-aid unit. Moreover, there seems no reason why divisions of the major first-aid organisations should not acquire manikins to hire out to individual units, which would spread the cost and ensure their maximum use. Even so, I submit that cost is relative, and the return in the saving of human life from wider use of oral methods of resuscitation will be inestimable.

The simplicity, effectiveness, and superiority of expired-air techniques have been well demonstrated [9]. The method has been universally adopted in the U.S.A. and in Switzerland. In New Zealand it is used by the Surf and Life-Saving Society and the Royal Life-Saving Society. It is also widely employed in Canada, Australia, Scandinavia, and elsewhere. Most significantly of all, it was officially adopted in October, 1959, by the Holger-Nielsen Committee of the Danish Red Cross, which

1. 2 *Kings*, iv, 34.
2. Taylor, S. First Aid in the Factory; p. 93. London, 1960.
3. International Convention on Life Saving Techniques, New South Wales. March, 1960.
4. Safar, P. *J. Amer. med. Ass.* 1958, **167**, 335.
5. Dobkin, A. B. *Lancet*, 1959, ii, 662.
6. Cox, J., Woolmer, R., Thomas, V. *ibid.* 1960, i, 727.
7. Croton, L. M. Royal Society for the Prevention of Accidents, press conference. May 23, 1960.
8. Saland, G., Collins, V. J., Preliminary Report on Field Experience with Mouth-to-Mouth Resuscitation (unpublished).
9. Council on Medical Physics: Symposium on Mouth-to-Mouth Resuscitation, 1958. *J. Amer. med. Ass.* 1958, **167**, 317.

was originally set up to popularise that method, which has now been abandoned in favour of the oral one. This committee has now been itself disbanded, and the " Elisha method " is everywhere taught in Denmark.

In face of such strong evidence in support of mouth-to-mouth artificial respiration, it is hard to understand why many first-aid workers fail to teach and practise it. Are they awaiting the findings of the M.R.C.'s working party, under Prof. Ian Donald, on emergency methods of resuscitation? I for one am confident that their conclusions will confirm those of the countries I have mentioned.

Department of Public Health, Bristol. ALEXANDER W. MACARA.

CLINICAL FEATURES OF PULMONARY EMBOLISM

SIR,—The article of April 8 by Dr. Barritt and Dr. Jordan prompts me to record certain observations I made on this condition over a period of some years in military surgical practice, where patients were usually but not always younger.

The first is that pulmonary embolism, either spontaneous or postoperative, appears with sufficient frequency in young people to emphasise the need to keep it in mind at all times. Another is that it is well worth paying strict attention to the complaints of the patient in the postoperative period, especially if there is some apparently unexplained pyrexia or tachycardia.

Pulmonary infarction can affect fit young men for no apparent reason. The only common factor noted in a group of such cases was recent strenuous exercise. The following is an example:

Overseas in 1952, a fit medical officer of 24, who was regularly playing good-class rugby, was admitted to medical wards because of right-sided basal pleurisy, followed by hæmoptysis. My interest in anticoagulant therapy was the reason for my being asked to see him. Only after careful cross-questioning did the patient provide the information that about a week before he had had some discomfort and aching in the right calf, of so little moment to his type as to be discounted and almost forgotten. Examination showed slight leg œdema, calf tenderness, and a positive Homan's sign, indicating the diagnosis and treatment. Moreover, this patient offered two pieces of information found to be of value in pointing to a diagnosis of thromboembolism and pulmonary infarction. For some nights before the hæmoptysis, he had difficulty with sleep and a feeling of being afraid—of what, he knew not.

I believe these two symptoms are important, so much so that in postoperative patients with some fever and tachycardia for no discoverable reason, who complain of sleeplessness and some bizarre fear, which they cannot describe or explain, I should suspect thromboembolism and its complications, and would not hesitate to give anticoagulants, even in the absence of more positive evidence, which in my experience will appear sooner or later.

Anatomy Department, University of Aberdeen. A. G. D. WHYTE.

SIR,—The article by Dr. Barritt and Dr. Jordan contains the traditional implication that pulmonary infarction is the almost invariable sequel of a pulmonary embolus. This prompts me to point out that while pulmonary emboli of varying sizes are only too frequently found during routine necropsies on patients who die in hospital, corresponding areas of pulmonary infarction are much less common.

The abnormal signs found clinically and radiologically in some cases of pulmonary embolus must thus be due to a lesion other than infarction—one, indeed, which resolves more readily than an infarction would be expected to.

When reviewing clinical and postmortem findings together, it is also apparent that some cases of pulmonary embolism may give rise to few or no abnormal physical signs in the lungs; the absence of such signs does not mean that a diagnosis of pulmonary embolism can be discounted, when other evidence, such as Dr. Barritt and Dr. Jordan mention, like a sudden episode of faintness, breathlessness, substernal pain, tachycardia, &c., is suggestive. The point is an important one, in view of the value—previously demonstrated by the same authors—of anticoagulant treatment after a first embolus.

Department of Pathology, Royal Alexandra Hospital, Rhyl, Flintshire. J. T. ALBAN LLOYD.

WHO IS DELIVERED?

SIR,—While agreeing with Mr. Russell (April 1) that there are many inconsistencies and inaccuracies in the use of the word " deliver " in midwifery, I question his statement that the verb is used intransitively. Surely to say that the mother is delivered is simply to use the passive of a transitive verb? If someone delivers the mother of her baby, or my bank manager reminds me of my overdraft, the object suffers the action of the verb in each case; and this applies no less when the mother is fortunate enough to deliver *herself* before any attendants arrive.

I agree that to speak of delivering the baby does not have the same biblical or historical precedent; but have we any verb to describe what is done to the baby? This may be the reason for the midwifery slang of my young days: " I borned a baby ". If there is no verb for this purpose, should we invent one? The infant-mortality rate of invented words is very high. Should we therefore agree to extend the use of " deliver ", so that, just as we deliver the mother *of* an increasing load, so we deliver the baby *from* its very constricted quarters. Even so, to say " she delivered a breech " is, as Mr. Russell suggests, absurd—I personally always made it my practice to deliver the whole baby—but this is only an extension of the unfortunate custom of calling one of our fellow creatures an appendix, a coronary, or a hallux valgus.

MIDWIFE.

SURGICAL TREATMENT OF DUODENAL ULCERATION IN HÆMOPHILIACS

SIR,—Dr. Handley and his colleagues (March 4) are to be congratulated upon successfully conducting major surgery on 2 patients with the help of antihæmophilic globulin of animal origin; but I wish to make it clear that my patient, to whom they refer, also underwent partial gastrectomy quite without incident or anxiety. The considerable amount of blood and blood products to which they refer was given entirely as a prophylactic measure immediately before operation and during convalescence until we felt that his wounds had completely healed.

My experience of this and a number of other patients who have undergone lesser surgical interference has led me to value human-blood products highly. We believe in daily or almost daily administration with, of course, the usual precautions against circulatory overloading.

We have found it easier to control patients with simple clean wounds and our greatest difficulties have arisen when patients, as a result of trauma, have developed deep-seated hæmatomas with extensive diffusion of blood into muscles and soft tissue. We have regarded evacuation of hæmatomas by aspiration or surgical drainage as contributing to improvement; and subsequent lavage with hypochlorite solution has seemed to help considerably.

There are obvious advantages in not sensitising patients by repeated injections of serum of animal origin; and I am writing to encourage preliminary intensive use of fresh human-blood products, at least as a first step, in dealing with hæmophiliacs requiring any form of surgical interference.

Royal Victoria Infirmary, Newcastle upon Tyne. T. H. BOON.

A TRISOMIC CHILD OF A HYPERTHYROID MOTHER

SIR,—5 different autosomal trisomies have so far been described in chromosomes (Denver system) nos. 21,[1–4] 17,[5] 15,[6] 19,[7] and 22.[8] We report a further trisomy in a seriously malformed child.

A full-term girl was born in St. Radboud Hospital on April 26, 1960 (figs. 1 and 2); her birth-weight was 3790 g., and length 50 cm.

The most noteworthy feature was the odd-shaped head with a very broad anterior fontanelle, due to a mild form of hydrocephalus. The nose-root was broad, and the eyes very far apart; the ears appeared low, but their shape was normal. There was a complete cleft palate and bilateral hare-lip, and, at the level of the lumbar vertebræ, a large meningomyelocele. The trunk was otherwise of normal shape, and so were the neck and extremities. Physical examination of the heart and lungs, and an electrocardiogram and chest fluoroscopy, revealed no abnormality.

On neurological examination a paresis of the lower extremities was found, and sensibility in these extremities was abnormal. Urination and defæcation seemed normal; the periodicity of these functions did not differ from that in other babies. The meningomyelocele was closed surgically; the hydrocephalus did not increase after the operation. The growth of the child, who was able to drink through a long nipple from a feeding bottle, proceeded normally. A plastic operation was recently performed to correct the bilateral hare-lip.

Fig. 1.

Fig. 2.

The child's mother, who was 41, was examined by us in the last two months of the pregnancy, her 3rd. Her first child, a girl weighing 3500 g., was born after eight years of marriage when the mother was 38. Two years later, another, with hydrocephalus and a meningocele, died during breech extraction. Both times the mother was noted to be moderately hypertensive, and a low-salt diet in the last two months of pregnancy was prescribed.

In our examination, we found a diffusely enlarged thyroid gland palpable in the neck. The blood-pressure (150/85 mm. Hg) was again somewhat increased, especially the systolic, and so was the pulse-pressure. The hæmoglobin level was 8·7 g. per 100 ml., and the hæmatocrit 30·4%; the serum-iron was 32 μg. per 100 ml., and the total iron-binding capacity 550 μg. per 100 ml. We treated her anæmia. The urinary glucose-test was positive. As the glucose-tolerance test revealed only doubtfully impaired glucose utilisation, these findings were consistent with renal diabetes of pregnancy. In view of the presence of a goitre and the increased pulse-pressure, the basal metabolic-rate was determined and found to be +35%. The serum-protein-bound iodine was 11·6 μg. per 100 ml., and serum-cholesterol 244 mg. per 100 ml.

Two months after her delivery the mother was again admitted to reinvestigate her glucose metabolism and thyroid-gland function. Glucose metabolism was normal, but the basal metabolism (+20%) was still raised. The serum-protein-bound iodine was 7·6 μg. per 100 ml., and the serum-cholesterol 193 mg. per 100 ml. The patient was given a tracer dose of radioactive iodine. Only 31·6% of the dose given was excreted in 48 hours, and the excretion pattern was typical of hyperthyroidism. The activity measured over the thyroid was consistent with the expected uptake. The biological half-life was 5 days. The protein-bound ^{131}I, determined at 72 hours, was 1·65% of the administered dose per litre of plasma. Thus hyperfunction of the thyroid gland was revealed.

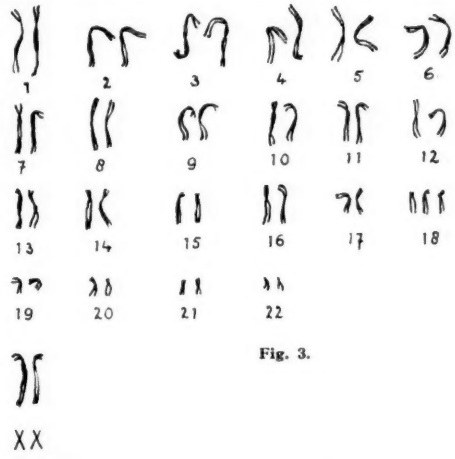

Fig. 3.

Smears from the buccal mucosa of the child showed a normal female sex-chromatin. Chromosomes were studied in cells from bone-marrow from the left tibia:

The specimen was processed by the direct method without a culture technique.[9] Immediately after puncture the material was collected in hypotonic solution, and then fixed for 10 minutes in 45% acetic acid. The marrow particles were squashed under high pressure on object glasses, and subsequently hydrolysed for 8 minutes in 1 *N* HCl at 60°C. After being washed in water the slides were stained in Feulgen reagent for one hour, and embedded in Canada balsam. As we did not use a culture technique the number of cells suitable for chromosome analysis was not very high. In this case 7 cells were found in which karyotyping could be performed.

The chromosome-count was invariably 47. After careful analysis in which the length and the location of the centromere were taken into account, 7 chromosomes appeared to belong to group 16–18 of the Denver system (fig. 3). In 3 of them the submedian position of the centromere was more distinct than in the other 4. These 3 chromosomes were tentatively classified as no. 18.

In the woman's family there are no cases of mental or physical defect. Her husband comes from a healthy farmer's family; he has a half-sister who is small and mentally defective, though her appearance is not mongoloid. The possibility that a hereditary factor caused these anomalies might be confirmed by examining the relatives' chromosomes.

The incidence of hyperthyroidism in pregnancy is relatively low, because a thyrotoxic woman is less likely to conceive than a normal one. But undoubtedly maternal

1. Lejeune, J., Gautier, M., Turpin, R. *C. R. Acad. Sci., Paris*, 1959, **248**, 602.
2. Jacobs, P. A., Baikie, A. G., Court Brown, W. M., Strong, J. A. *Lancet*, 1959, i, 710.
3. Ford, C. E., Jones, K. W., Miller, O. J., Mittwoch, U., Penrose, L. S., Ridler, M., Shapiro, A. *ibid.* p. 709.
4. Book, J. A., Fraccaro, M., Lindsten, J. *Acta pædiat., Uppsala*, 1959, **48**, 453.
5. Edwards, J. H., Harnden, D. G., Cameron, A. H., Crosse, V. M., Wolff, O. H. *Lancet*, 1960, i, 787.
6. Patau, K., Smith, D. W., Therman, E., Inhorn, S. L., Wagner, H. P. *ibid.* p. 790.
7. Fraccaro, M., Kaijser, K., Lindsten, J. *ibid.* p. 724.
8. Hayward, M. D., Bower, B. D. *ibid.* 1960, ii, 844.
9. van Brink, J. M. L'expression Morphologique de la Digamétie chez les Sauropsidés et les Monotrèmes. Thesis, University of Utrecht, 1959.

thyrotoxicosis injures the fœtus.[10] Abortions, prematurity, stillbirths, and neonatal deaths are common. In an earlier series, in one-half of the pregnancies the fœtus died.[11] We failed to find any data in the literature on the incidence of congenital defects in the children of thyrotoxic mothers, such as are described for myxœdematous women.[12] We wonder whether maternal thyrotoxicosis does harm at an earlier stage of reproduction—e.g., at oogenesis. Perhaps live children with congenital anomalies to support this suggestion are lacking precisely because these pregnancies abort. We wondered therefore whether the mother's hyperfunctioning thyroid gland might be related to the non-disjunction in this child, and to the birth of the other abnormal child. If this assumption is correct, it might be advisable to investigate the mothers of trisomic children (with the possible exception of mongols [13]) for thyroid dysfunction.

J. A. M. VAN WIJCK
L. A. M. STOLTE
H. I. A. M. VAN KESSEL
G. A. J. TIJDINK.

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DIAGNOSIS OF ACUTE APPENDICITIS

SIR,—With Mr. Bevan's recent comments (Feb. 18) in mind, I recently diagnosed acute appendicitis in a patient whose cæcum gurgled markedly on palpation. I removed an acutely inflamed appendix—there being no other abnormality as far as could be found through a McBurney's incision. I have heard of this diagnostic point before, and have a distinct recollection of having removed at least one other acutely inflamed appendix in the presence of a gurgling cæcum.

As with so many signs of appendicitis, I feel it would be injudicious to be dogmatic about any one of them. Surely it is preferable to relate a single sign to the clinical findings as a whole.

Royal Air Force Hospital, Ely.

D. M. ESSENHIGH.

RENAL TUBULAR ACIDOSIS

SIR,—You published a letter from Dr. Rakitzis (Feb. 25) which took exception to statements in your leading article (Jan. 14). I myself disagree mildly with one expression in your leading article, and strongly with Dr. Rakitzis' letter.

You stated that " Hydrogen ion is eliminated in two forms—(1) as free hydrogen ion . . . and (2) as ammonium ion ". I am sure that you did not in fact mean " free " hydrogen ion, as only a very minute amount indeed of hydrogen can leave the body as free hydrogen in the urine (e.g., 0·1 mEq. in a litre of urine at pH 4.) Most of the hydrogen ion excreted in an acid urine with phosphate is as effectively bound as that excreted attached to ammonia, even though the pK_A of the latter species gives the ammonia a clear advantage in affinity for the protons.

Surely it is correct to say that ammonium chloride and sodium bicarbonate cause metabolic acidosis and alkalosis *only* because they are a proton donor and acceptor respectively. It is also true, as your correspondent states, that " the administration of ammonium chloride or sodium bicarbonate is thus in effect equivalent to hydrochloric acid or sodium hydroxide intake ", but can this be for any other reason than that there are hydrogen ions as part of the NH_4^+ of ammonium chloride, and hydroxyl as part of the HCO_3^- of sodium bicarbonate? (His statement would not be less true if he had used ammonium nitrate and calcium bicarbonate, " equivalent to " nitric acid and calcium hydroxide.) If acidosis is by definition an abnormally high concentration of hydrogen ion in the serum, then it must take hydrogen ion to produce it, and removal of hydrogen ions or their neutralisation with hydroxyl ions to decrease it. It is difficult to see how " fixed " anions and cations have anything to do with the case beyond their role as " spectator " ions.

Bethesda, Maryland. F. C. BARTTER.

LIVER-PALMS AND FRONTAL-LOBE TUMOURS

SIR,—The common association of " liver-palms " with cerebral tumours involving the frontal lobes has not hitherto been described.

Of 100 patients with frontal-lobe tumours seen in three years, rather under half had abnormal palmar erythema. While the interpretation of this must vary from observer to observer, probably 40% of these patients would be generally accepted as having liver-palms.

The appearance of the hands, and of the soles of the feet, which are also often affected, is indistinguishable from that in chronic liver-failure. But in the neurological patients the results of usual liver-function tests were normal; and in those cases coming to necropsy general liver-disease was not observed (though several patients had metastases in otherwise healthy livers).

Both hands were always affected equally, and the tumours might be in either hemisphere or in both; and liver-palms were seen in association with all types of neoplasms except meningiomas, either of the convexity or of the olfactory groove.

Liver palms have been observed in many conditions—in particular, in chronic hepatocellular failure, and rheumatoid arthritis. Sherlock [1] describes the changes as follows: " The hands are warm and the palms bright red in colour, especially the hypothenar and thenar eminences and the pulps of the fingers. Islets or spots of erythema may be found at the bases of the fingers. The soles of the feet may be similarly affected." The degree of erythema seems to bear no constant relationship to reduction or alteration in serum-proteins, or to deranged liver function; and its cause is unknown. It may be due to some deficiency state, or to impaired metabolism of œstrogens.

Presumably the change in the palms is caused by a disturbance of the autonomic nervous system. But, though the prefrontal association areas are assumed to take part in regulating autonomic function, no prefrontal cortical autonomic centres for the *focal* control of vascular or sweating responses have been demonstrated. Changes in sweating after prefrontal leucotomy seem merely to reflect the general improvement in the patient's health—i.e., there is increased palmar sweating when the operation was performed for depression, and decreased sweating when it was for agitation. Palmar erythema has not been observed.

The explanation for this must depend on the position of the lesion. The tumours with which liver-palms are associated are gliomatous and metastatic growths within the substance of the hemisphere, and development of erythema is a fairly late sign; in other words, there is extensive damage well back in the frontal lobe. With meningiomas, there is not as a rule so much destruction, and no palmar changes occur.

In chronic liver-failure, the first sign of cerebral involvement is the appearance in the E.E.G. of slow waves in the frontal region. At the time this becomes clinically apparent, the patient often shows just those signs of disinhibition and loss of insight which characterise frontal-lobe lesions. The frontal slow waves, and the mental changes, have been supposed to result from a toxic disturbance of deep midline brain structures. It may be that the frontal areas of the brain themselves are very sensitive to the hepatic state—with liver-palms as a secondary effect.

The observation is of little value in diagnosis; for by the time palmar erythema appears, other indications of a frontal-lobe lesion will already have been noted. But it

10. Silver, S. Complications of Pregnancy. Baltimore, 1960.
11. Mussey, R. D., Plummer, W. A., Boothby, W. M. *J. Amer. med. Ass.* 1926, **87**, 1009.
12. Hodges, R. E., Hamilton, H. E., Keettel, W. C. *Arch. intern. Med.* 1952, **90**, 863.
13. Copper, A., Cowie, V. *Brit. med J.* 1960, i, 1843.

1. Sherlock, S. Diseases of the Liver and Biliary System. Oxford, 1958.

may be useful in differential diagnosis: its presence suggests that a space-occupying lesion in the frontal lobe is unlikely to be a meningioma.

Department of Neurology,
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London, E.1. J. C. PHEMISTER.

HOSPITAL DOCTORS

SIR,—On reading the description in the Platt report of the proposed new grade of medical assistant, one is struck by the remarkable similarity between this grade's proposed status and duties, and those of the permanent top-scale J.H.M.O. The latter has long experience of a specialty but is always, in theory at least, under the supervision of a consultant. The numbers permanently in this grade are very small indeed and some years ago they realised their chances of getting similar jobs elsewhere had vanished, without warning, as no more permanent J.H.M.O.s were being appointed.

I count among my colleagues a J.H.M.O. who until recently ran a mass X-ray unit, and another in day-to-day charge of a laboratory; and I was myself originally appointed to the honourable grade of assistant medical officer in the London County Council hospital service. I feel therefore that our senior negotiators and representatives should know more of the work and plight of permanent J.H.M.O.s.

J.H.M.O.

SIR,—Concerning the shortage of British doctors, I am surprised that no-one has mentioned the fact that there are many married women doctors who are unemployed and who would welcome part-time posts such as clinical assistantships. It seems a pity that these are usually given to local general practitioners, who are already overworked.

I am one of these and have strongly thought of school-teaching, where married women are welcome part-time; at times I have even considered delivering soap-powder coupons, which seems a waste of 6 years' medical training! There are some openings for part-time work in general practice, but the hours are not usually convenient for a housewife; and in clinics more and more work is arranged on a full-time basis.

University posts such as demonstratorships are not easily obtainable and are only very rarely part-time. More clinical assistantships would be welcomed by housewives who wish to continue in practice and would at the same time help to solve the national shortage of doctors.

Purley, Surrey. UNDERWORKED.

PROTEIN-LOSING ENTEROPATHY

SIR,—With reference to the paper of Dr. Jarnum and Dr. Peterson (Feb. 25), I would like to add that a protein-losing enteropathy together with fat malabsorption may be observed in advanced hepatic cirrhosis.

We performed an absorption test with ^{131}I-labelled oleic acid on 5 such patients and found considerable impairment of oleic-acid absorption in each case. The mean 48-hour stool excretion of oleic acid was 25·3% of the administered dose, with a range of 19·6%–26·0% (normal mean 2·8%, with a range of 0·3%–5·2%). The mean peak whole-blood radioactivity was 1·04% of the administered dose per litre of blood, with a range of 0·39%–1·36% (normal mean 2·3%, with a range of 1·77%–2·76%).

Fat malabsorption associated with cirrhosis has been attributed to concomitant pancreatic disease and consequent deficiency of pancreatic enzymes.[1] The results of the oleic-acid study, however, point to dysfunction of the small intestine, as oleic acid is absorbed by the small intestine without the aid of pancreatic lipase. Abnormalities in the duodenal and jejunal mucosa have been reported in advanced cirrhosis. These pathological changes were most likely related to portal hypertension.[2]

Protein may leak through such a mucosa. When intravenous ^{131}I-labelled albumin was given to one of the above patients by Prof. A. De Vries, head of medical department D., Beilinson Hospital, much of the labelled albumin was lost in the stool, and albumin rapidly appeared in the peritoneal cavity.

Many of the biochemical abnormalities in advanced cirrhosis, such as the low serum-carotene and vitamin-A level, and the increased prothrombin-time, may be related to fat malabsorption as well as to intrinsic liver disease. A protein-losing enteropathy may contribute to the hypoalbuminæmia of hepatic cirrhosis. Further studies are in progress to clarify these relationships.

Department of Radioisotopes,
Beilinson Hospital,
Petach Tikvah, Israel. MELVIN JAY SCHWARTZ.

1. Fast, B. B., Wolfe, S. J., Stormont, J. M., Davidson, C. S. *Gastroenterology*, 1959, **37**, 321.

BEHAVIOUR THERAPY IN A CASE OF TRANSVESTISM

SIR,—Dr. Barker and his colleagues (March 4) described their treatment of a case of transvestism, and expressed some doubts whether the patient's improvement was due to deconditioning. Furthermore, they criticised the method used in terms of expense, unpleasantness to the patient (and why not also to the therapist?), and length of treatment.

I hope the following rather different case-report may stimulate further debate on the factors contributing to a patient's recovery. The method, incidentally, did not have the disadvantages of which Dr. Barker complained.

A 17-year-old boy was brought to the psychiatric clinic by his father because the police found him wandering on the local common dressed in his mother's underclothes, rubber shoes, and a plastic waterproof. His first episode of transvestism had been at the age of 9 when the family moved to London. The patient had felt extremely isolated since his friends had been left behind. His only occasional companion had been a girl cousin whom he envied because of her great ease in social relationships. It was this girl's clothes he had first put on as they enabled him to imagine he was garbed with her personality. Since that time he had regularly dressed up in feminine clothes, usually his mother's, as they were close to hand. He said that he had dressed in women's underclothes and walked around the common on one previous occasion, and got back home without being noticed. He insisted that whilst dressed up he felt at ease with the world, imagining he was a sociable girl. He was grossly ignorant of sexual matters and had no homosexual inclinations or phantasy.

He had a younger brother of 5. He had a few minor neurotic traits as a child and left grammar school at the age of 15 because of difficulties. He disliked the discipline, felt he was picked on by one of the masters, and frequently played truant and told lies. He was now working in a surveyor's office and attending night school in order to sit his G.C.E. His full scale I.Q. (Wechsler) was 112, but this was thought to be a low estimate. The psychologist found him so shy that she constantly had to repeat questions because she could not hear what he said; and she commented on his considerable disjunction with the world. Certainly he felt at a distance from his parents emotionally, had few friends, and no interests except football.

His central problem was considered to be one of isolation and an inability to make close rewarding relationships with others. His perversion was seen as an aspect of this primary difficulty. In fact much support was found to bear out the existential views of Medard Boss [3] on sexual perversion. It was predicted that if the boy was helped out of his isolation his perversion would improve pari passu.

At the first interview I saw both the patient and his father. I

2. Astaldi, G., Strosselli, E. *Amer. J. dig. Dis.* 1960, **5**, 603.
3. Boss, M. Meaning and Content of Sexual Perversions. New York, 1949.

suggested to the boy that if he personally wished for my help I would see him at fortnightly intervals for an hour on each occasion, unaccompanied by his father. Including the initial interview he was seen on 6 occasions. Psychotherapy aimed at helping him to communicate with me, and through our relationship to understand his difficulties such as those with authoritarian figures. 1 session was taken up with a discussion of sex, which was placed firmly in the context of a love relationship. After the third interview the father came to see me in a state of great alarm. He had gone to his son's bedroom and found him standing naked except for a woman's jumper. His son admitted taking the jumper from a neighbour's clothes line. Evidently the father's first thought had been to phone the police because of his "obligation to society"! The mother, however, suggested the jumper should be returned to the clothes line, and that the father should tell me about the matter. The opportunity was used to discuss with the father the distance he caused between himself and his son by his cool authoritarianism. Such was the impression caused by our talk that the father went home and had a heart-to-heart discussion with his son, which made a great deal of difference to their relationship.

At the sixth interview the boy was talking easily and freely with me, and said that on his own initiative he had joined a mixed club and was playing football for a club. He had made many friends and was going out to parties. He had no inclinations to dress up in women's clothes at all. Seven weeks later he was seen for review and said that he was feeling very happy and well. He continued with his active social life and was enjoying the company of girls at the club outings. Although the period of follow-up was short, the quality of the improvement was striking not only to myself but to his parents.

What were the factors which contributed to the improvement of Dr. Barker's patient and mine? Was there a common denominator or were both our approaches suitable for particular therapists with particular patients? Shoben [4] would probably suggest that my therapeutic endeavours could be interpreted in the light of learning theory. Is it not time there was some rapprochement between behaviour therapists and other psychotherapists? Each could make contributions to the therapeutic process from seemingly very different points of view.

St. George's Hospital, London, S.W.1. IAN J. MACDONALD.

REPRINTS

SIR,—Dr. Faulds' experiences with reprint requests (Feb. 11) are indeed not unique. Most requests we receive from abroad come on printed cards; and I believe that this form of communication is not discourteous, but efficient and sound.

I am not entirely clear why Dr. Faulds objects to cards; but he seems to attribute the apparent increase in reprint requests to their use. This is not necessarily the case. Many new laboratories have been established in America during the past decade and subscribe to only a limited number of journals. Reprints thus facilitate research coverage and planning, and also the preparation of articles.

Requesting two or even three reprints does not seem at all irregular to me. We may request two or three reprints of significant papers so that our library (which may not have the journal) will have a copy, and an associate who is actively working in the field can also be supplied expeditiously. When we receive a request for two or three reprints we regard it as a compliment, and a multiple request from us is also intended as a compliment.

The attitude of Dr. Farnan (Feb. 18) is surely the antithesis to the cooperative spirit that should prevail in the scientific community; and I believe it represents a deterrent to scientific progress.

4. Shoben, J. S. *in* Behaviour Therapy and the Neuroses (edited by J. H. Eysenck). London, 1960.

I wish to defend the use of printed cards for requesting reprints, on the grounds of simplicity and efficiency. Unless there are specific comments or personal communications to be included in the request, personal letters are much too time-consuming for both sender and recipient.

Richland, Washington, U.S.A. LYNN A. GEORGE.

BUFOTENIN IN HUMAN URINE

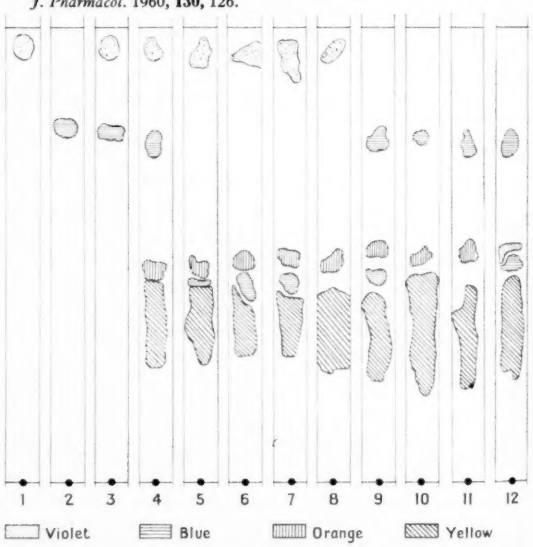
SIR,—In his recent survey of the biochemistry of psychosis, Dr. Smythies [1] stated that a method [2] capable of detecting as little as 3 μg. per ml. urine identified no bufotenin and N-methyltryptamines in the urine of schizophrenics.

Nevertheless, Bumpus and Page [3] found N-methylserotonin and bufotenin in normal human urine by a rather complicated and cumbersome method.

We have developed a simple method to detect indole bases in human urine. 1 litre of urine is saturated with sodium carbonate and then extracted twice with butanol, 500 ml. in all. In future, this extraction may be replaced with advantage by continuous extraction in a Soxhlet apparatus for 3 hours.[4] The butanol extract is then concentrated to dryness in vacuo and the residue extracted with a small volume of acetone. The acetone is evaporated and the residue is dissolved in 1·0 ml. of absolute acetone. 0·1 ml. of this extract is placed on a paper strip (Whatman no. 1), chromatography is carried out for 20 hours with butanol-ammonia and staining by 2% acid aqueous solution of *p*-dimethylaminobenzaldehyde.

We tested the urine of 5 hallucinated schizophrenics and 4 others without mental disturbances. The figure shows that known bufotenin appeared constantly as a spot of dark violet colour of R_F 0·93. (The samples were obtained by courtesy of Upjohn, Geigy, and Sigma.) A known sample of serotonin showed a blue spot of R_F 0·76. Each of the urine extracts of the 5 hallucinated schizophrenics assayed by paper chromatography showed spots apparently identical with those

1. Smythies, J. R. *Lancet*, 1960, i, 1287.
2. Rodnight, R. *Biochem. J.* 1956, **64**, 621.
3. Bumpus, F. M., Page, I. H. *J. biol. Chem.* 1955, **212**, 111.
4. Gessner, P. K., Khairallah, P. A., McIsaac, W. M., Page, I. H. *J. Pharmacol.* 1960, **130**, 126.



(1) Chromatogram of bufotenin, R_F 0·93. (2) Chromatogram of known serotonin, R_F 0·76. (3) Chromatogram of a mixture of known bufotenin and serotonin. (4-8) Chromatograms of the urine extracts of five schizophrenics. (9-12) Chromatograms of the urine extracts of four normal persons. The yellow spot is urea, with a R_F value of 0·35. There are also two unidentified spots, a blue one at R_F 0·45 and an orange one at R_F 0·50.

of bufotenin (R_F, colour, time of appearance); whereas the chromatograms of the urine extracts of the 4 without mental disturbances did not.

We are certain that the substance which behaved chromatographically as bufotenin could be determined quantitatively in the final acetone extract by spectrofluorometry. Unfortunately, we do not have a suitable apparatus; but by comparison with a scale of different amounts of pure bufotenin we estimated the quantity of presumptive bufotenin in the schizophrenic urines investigated as approximately 0·4 mg. per litre.

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NEONATAL VARICELLA

SIR,—The article by Dr. Readett and Dr. McGibbon (March 25) prompts me to report an interesting case seen here.

A woman who had had two children, was admitted in labour; she had had typical chickenpox lesions for two weeks. These were now in their final stages; the infection had been contracted from her young daughter. Her confinement was normal; a 6-lb. live girl was born. Within two hours typical chickenpox lesions developed on the baby's scalp, back, and lower limbs. At ten days the lesions are clearing, and there have been no complications.

Risedale Maternity Hospital, Barrow-in-Furness. ALAN BERTRAM.

SIR,—The recent article by Dr. Readett and Dr. McGibbon prompts me to report this case.

Mild varicella developed in a woman seven days before her full-term infant weighing 7 lb. 3 oz. was born. Soon afterwards she received 20 ml. of γ-globulin; and the skin lesions had cleared by the time of delivery. The baby was given 4 ml. of γ-globulin within 24 hours of birth. Two days after discharge from hospital at the age of seven days the typical skin lesion of varicella developed in the child. The course was entirely benign.

Attenuation of chickenpox by γ-globulin has been reported [1]; and passive immunity conferred either by the mother via the placenta or by γ-globulin may have been responsible for the benign course in this case.

Beth Israel Hospital, Boston, Massachusetts. LONNIE HANAUER.

PNEUMOTHORAX ACCOMPANYING STAPHYLOCOCCAL PNEUMONIA IN PATIENTS TREATED WITH STEROIDS

SIR,—The recent paper by Dr. Olesen and Dr. Quaade (March 11) on the development of pneumothorax in patients receiving steroids was timely, interesting, and important.

At the time their article appeared we had under our care a 3-year-old child with aplastic anæmia who had received 200 mg. of cortisone for ten days. A left-sided tension pneumothorax developed without any clinical symptoms whatever, and was detected by auscultation during a routine examination. 200 ml. of pus from which *Staphylococcus aureus* was cultured was drained from the thorax, and the patient recovered.

During the past 5 years we have used corticosteroids to treat more than 300 children with hæmatological disorders and have not observed this complication until now.

While the underlying mechanism is obscure and unexplained, undoubtedly corticosteroids may profoundly alter the clinical symptoms of pneumothorax and so make it difficult to diagnose except by physical examination.

Children's Medical Service, Massachusetts General Hospital, Boston. JOSEPH J. MCGOVERN.

1. Trimble, G. X. *Canad. med. Ass. J.* 1957, **77**, 697.

HARSH TREATMENT?

SIR,—Remembering my own confinements, I sometimes wonder if we are not being unfair to our young mothers by sending them home so soon after delivery to cope with a new baby, a husband (sometimes jealous of the baby), cooking and washing, and perhaps a toddler (also jealous of the new arrival).

I have lately heard of cases of depression among girls who before their confinement were too full of the happiness of married life, husband, and the prospect of a baby to know the meaning of the word. In hospital they were got on their feet on the second or third day after delivery, walked to the bathroom, had to bath themselves and the baby, and were left with it all night—crying. In my own confinements many years ago all responsibility was taken from my shoulders by a resident monthly nurse. Even so, when I took over the reins of running the household, with the addition of the baby and all the extra washing that implies, I found it difficult enough.

Girls are now becoming mothers at an earlier age and I fear that we are not giving due heed to their emotional state, weakness, and inability to cope after a confinement. The district nurses are wonderful, but I am concerned about the mental as well as the physical health of the mother.

Would it not be possible to have a kind of annexe to the hospital where mothers could spend some days with their babies happily regaining strength before going to their homes? I feel strongly about this because I have come across several young wives who dread the prospect of having a second child because of their difficulties after the birth of the first.

Uxbridge, Middlesex. ETHEL RAMSAY.

POSSIBLE TERATOGENIC EFFECT OF TOLBUTAMIDE IN PREGNANCY

SIR,—The paper of Dr. Larsson and Dr. Sterky [1] prompts me to record that in the diabetic clinic of the King Edward VIII Hospital in Durban we are now giving the sulphonylureas routinely to about 90% of our pregnant Natal Indian diabetics, and to control patients who develop glycosuria in pregnancy.

These pregnant diabetics represent a recently described tropical variant of diabetes [2] referred to as the "insulin-independent young diabetics"; they do not depend on exogenous insulin in the ordinary course of events, even though they present with the classical symptoms of diabetes (but they never become ketotic). They are even able to overcome superadded infection without insulin, and in some of them induction or cæsarean section can be performed without it. A satisfactory response to sulphonylureas, with no response to such dietary restriction as we are able to impose, is a sine-quanon for the diagnosis of "insulin-independent young diabetic". These patients make up 16% of the Natal Indian diabetics, and they are most commonly in their early twenties at the onset of diabetes.

So far we have taken 21 such insulin-independent young pregnant diabetics (excluding pregnancy glycosurics) through pregnancy with a fœtal loss of 5—including 1 grossly malformed congenitally. Its mother had a most unsatisfactory obstetric history: her 1st fœtus died in spite of insulin control, her 2nd in spite of combined tolbutamide and insulin control, and her 3rd, described above, being lost after what was really very satisfactory control with tolbutamide alone. I do not believe it is possible to determine the part the drug played in these malformations. Against the possibility is the mother's bad history: it is interesting that in this small series it was only in this patient with the worst history that teratogenesis was found.

The problem of fœtal malformations due to sulphonylureas is going to become very important in future: firstly, because these drugs are bound to be given increasingly to alleviate

1. Larsson, Y., Sterky, G. *Lancet*, 1960, ii, 1424.
2. Campbell, G. D. *Brit. med. J.* 1960, ii, 537.

pregnancy glycosuria; and secondly, their success in pregnant diabetics will prompt us to administer them more widely in our fast-growing clinic. We predict that the sulphonylureas will be extensively used in the tropics to treat pregnant diabetics (especially since tropical diabetes is generally mild) and more particularly in certain dark-skinned races (notably Asiatics) who might fall into the category of the insulin-independent young diabetic: in a small series of these pregnant patients we have found that the sulphonylureas can supplant insulin in over 90%.

Thus it is most important for those intending to give these drugs to know whether they can cause fœtal malformations; it is to be hoped that any further cases will be promptly reported.

Diabetic Clinic,
King Edward VIII Hospital,
Durban, Natal.

G. D. CAMPBELL.

CHANGES IN BLOOD AND URINE α-AMINO-NITROGEN CONCENTRATION IN PREGNANCY

SIR,—It has been shown [1] that the excretion of lysine in certain pregnancy diseases is significantly increased. At the time interpretation was hampered by inability to estimate blood-lysine levels; for this reason, and because the changes in lysine excretion may only reflect disturbances of other aminoacids, the α-amino-nitrogen concentration of blood and of a 24-hour urine specimen was simultaneously measured.

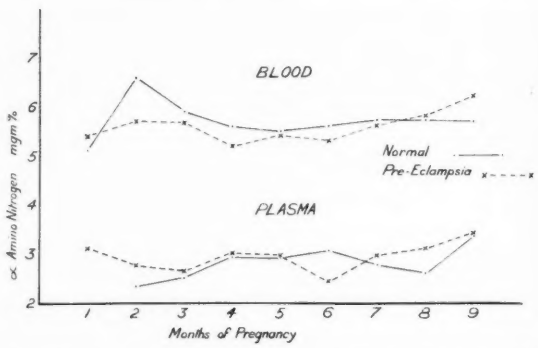
The α-amino-nitrogen concentration was measured in the urine by the method of Albanese and Irby [2] and in the blood by the method of Krauel.[3] Later, estimations were made on plasma to eliminate possible variations due to alterations in the cell-content of aminoacids.

The method of Albanese and Irby has been reinvestigated by Schroeder and his colleagues [4] who showed that phosphate concentration in the reacting medium was critical, and that lysine was necessary to form soluble complexes with certain aminoacids. The differences resulting from variations in these and other substances in the urine have been measured and are very small when compared with the changes found in our investigation.

TABLE I—URINARY α-AMINO NITROGEN (mg. per day × 1/10)

Group	Case	Month								
		1	2	3	4	5	6	7	8	9
1 Normal pregnancy	A	..	35	39	48	33	44	40	..	31
	B	18	34	30	36	38	29	37	31	..
	C	..	20	10	6	18	31	34	34	36
	D	..	..	..	65	50	..	..	..	31
	E	..	..	37	31	32	46	45	90	39
	F	..	34	38	39	48	41	51	28	27
	G	..	..	..	40	40	37	40	37	31
	H	..	..	..	..	42	39	47	80	..
	I	52	44	52	38	43	39	47	50	48
	J	..	48	79	42	50	30	..	88	..
	K	35	49	51	46	63	49	55	63	49
2 Pre-eclampsia	L	..	27	33	37	16	63	30	54	29
	M	..	..	..	45	20	13	46	35	15
	N	..	48	70	55	78	107	63	54	76
	O	..	..	..	..	..	55	48	66	41
	P	..	..	..	38	38	49	48	58	43
	Q	..	36	53	43	50	50	67	62	39
	R	..	50	54	48	45	53	47	42	59
	S	..	44	46	53	48	57	36	32	..
	T	..	..	66	57	54	64	71	66	88
3 Placental insufficiency	U	..	..	..	..	..	63	61	59	65
	V	..	38	52	57	65	67	69	56	54
	W	55	52	52	63	40	49	38	50	..

We have described the clinical material previously.[1] α-amino-nitrogen excretion in the urine is shown in table I. This is much more variable than lysine excretion, but despite this the 3 groups (*a*) normal pregnancy, (*b*) pre-eclampsia, and (*c*) placental insufficiency, differ significantly in their overall mean values and in the same order as found with lysine. But dissimilarity between these 3 groups does not appear as early in pregnancy as with lysine. We conclude that the determination of urinary lysine reflects more accurately the state of the other aminoacids.



Blood and plasma α-amino nitrogen (table II and figure) remain remarkably constant throughout pregnancy, implying a high degree of homœostasis. Levels are lower than in non-pregnant women (6·6 to 12·4 mg. per 100 ml. blood [3]), but rise to these within one week of delivery.

The absence of a difference in blood and plasma α-amino nitrogen in normal pregnancy and pre-eclampsia, despite significant differences in urinary excretion, suggests at first sight a renal cause of the aminoacid loss.

TABLE II—BLOOD AND PLASMA α-AMINO NITROGEN (mg. per 100 ml.)

Group	Case	Month									
		1	2	3	4	5	6	7	8	9	10
Normal pregnancy blood	1	..	8·6	6·2	5·0	5·3	5·7	5·5	6·1	6·0	..
	2	..	..	..	6·0	5·8	5·9	5·8	5·7	5·3	..
	3	..	..	..	..	5·8	5·5	5·6	5·8	..	..
	4	5·1	5·3	5·6	5·5	5·7	5·4	5·9	5·4	5·5	..
	5	..	6·0	6·1	5·5	5·6	6·1	..	5·6	..	..
	6	..	6·0	5·6	5·2	5·4	5·3	5·5	5·5	6·1	..
Pre-eclampsia blood	7	..	5·4	5·8	5·8	5·7	6·1	5·5	5·8	5·4	6·2
	8	..	5·5	5·2	5·2	6·0	5·7	5·9	6·8	6·8	..
	9	..	..	..	..	..	4·9	4·0	5·6	5·9	6·8
	10	..	..	..	4·6	4·4	5·3	5·2	5·1	5·0	..
	11	..	6·0	5·3	5·4	6·0	5·7	6·0	6·2	..	..
Placental insufficiency blood	12	..	..	..	..	..	5·5	5·2	5·6	5·7	..
Normal pregnancy plasma	13	..	1·73	1·86	2·79	2·73	3·34	2·91	2·79	4·21	..
	14	..	1·86	2·11	3·10	..	2·98	2·29	2·48	3·22	..
	15	..	..	..	..	..	..	..	..	..	2·48
	16	..	..	..	2·98	2·91	2·85	2·85	2·48	2·73	3·16
	17	..	..	3·45	2·98	2·97	3·10	2·97	3·41	2·42	3·72
Pre-eclampsia plasma	18	..	..	1·86	1·74	2·98	2·92	2·73	2·98	3·10	3·47
	19	..	..	..	2·91	..	1·80	3·10	3·04	3·10	..
	20	..	3·10	3·60	3·16	2·98	2·73	2·73	2·60	3·41	3·55
	21	..	..	..	2·98	2·91	3·10	2·53	3·22	2·81	3·60
Placental insufficiency plasma	22	..	..	3·72	2·60	2·60	2·98	2·36	2·73	3·16	2·85
	23	..	2·04	2·23	2·79	1·55	2·79	3·41	2·29	3·41	..

A possible lack of utilisation of aminoacids by liver, placenta, or fœtus, with the kidney having a passive role with a set level of reabsorption, must, however, be considered. It is more likely that factors which influence utilisation also interfere with renal reabsorption so that urinary excretion of aminoacids may become a very sensitive index of overall interference in protein catabolism.

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F. M. C. FORSTER
A. M. SMITH.

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* King George V Jubilee Research Scholar.

1. Bolton, J. H., Forster, F. M. C., Kerley, L. F. *Lancet*, 1960, ii, 345.
2. Albanese, A. A., Irby, V. *J. biol. Chem.* 1944, **153**, 583.
3. Krauel, K. K. *J. Lab. clin. Med.* 1944, **29**, 222.
4. Schroeder, W. A., Kay, L. M., Mills, R. S. *Analyt. Chem.* 1950, **22**, 760.

LOWERING BY PREDNISONE OF SERUM-CALCIUM IN HYPERPARATHYROIDISM

SIR,—Though most tests used to diagnose primary hyperparathyroidism may give false-negative results, the lowering of serum-calcium level by a glucocorticoid is usually considered very reliable in excluding this disorder. This test appeared to fail us in the following case.

A white woman of 63 had a calcium-oxalate stone removed from her left kidney by Dr. P. J. M. Retief in August, 1960. The serum-calcium level was found to be high; so she was subsequently admitted to Groote Schuur Hospital for investigation.

She was not wasted, not in any way ill, and showed no indication of sarcoidosis or malignant disease. She had not been taking calciferol. Serum-phosphorus levels ranged between 3·3 and 3·8 mg. per 100 ml. Alkaline-phosphatase, blood-urea, serum-protein, and electrolyte levels were normal; blood-examination revealed no abnormalities. Skeletal X-rays and examination by barium-swallow were also normal. Her 24-hour urinary calcium totalled about 350 mg. Renal tubular reabsorption of phosphorus (based on two 2-hour clearance tests, with endogenous creatinine clearance to measure glomerular filtration-rate) was 92 and 95%. The urine was acidified to pH 4·5 after a single dose of ammonium chloride. Prednisone, in doses of 20 mg. b.d., was given for 12 days, and the serum-calcium readings were as follows:

Day	*Serum-calcium (mg. per 100 ml.)*	*Day*	*Serum-calcium (mg. per 100 ml.)*
Prednisone started		8	10·9
1	12·3	9	11·2
2	12·0	11	11·4
3	11·2	Prednisone stopped	
5	11·0	13	11·2
6	11·2	15	10·9
		17	11·0

We were unable to carry out the test again. Despite these findings, the parathyroid glands were examined by Dr. R. Lane Forsyth in November. The left lower gland was found to contain a tumour the size of a pea, which was removed. Histological examination revealed a chief-cell parathyroid adenoma. Two weeks after operation the serum-calcium level was 9·4 mg. per 100 ml. and the serum phosphorus 5·0 mg. per 100 ml.

The serum-calcium estimations were performed in our endocrine laboratories by the method of Greenblatt and Hartman.[1] In a double-blind test in our laboratory we found this subject to an error of less than 2% either way. The upper limit of normal for serum-calcium readings we take as 11·0 mg. per 100 ml. (99 percentile).

We think that the reduced serum-calcium level while the patient was on prednisone may have been fortuitous.

Groote Schuur Hospital,
University of Cape Town,
South Africa.

W. P. U. JACKSON.

NEW STANDARDS FOR ESTIMATING BONE DENSITY

SIR,—Dr. Koch and Dr. Kaplan (Feb. 18) recommended the use of open-ended stainless-steel tubes filled with various amounts of bone as new standards for the estimation of bone density. Such standards have been used before, and detailed studies made of their value.

I have used small 'Perspex' boxes filled with different amounts of bone powder and human finger bones removed at necropsy as standards to determine the mineral content of finger bones.[2] In order to avoid the distributional error [3]—very important in this connection—silver analysis of the X-ray film was performed instead of optical densitometry.

The accuracy of visual estimation of bone density is too low to be of much practical use, although special phantom bones are used as standards.[4 5] If evenly absorbing standards are used, as proposed by Koch and Kaplan, the measurement of bone density is still more unreliable because of the uneven distribution of the bone minerals and the covering effect of the soft tissues in and around the bone.[6] Even if the densities of the standards are objectively measured by point densitometry and compared with the densities of the bones to be examined, the method is inaccurate.[2 7] It is therefore not surprising that the amounts of apatite in the standards used by Koch and Kaplan were considerably higher than the actual mineral content of normal finger bones.[2 8]

Attractive as it would be to express the results of radiographic examination in terms of bone density, it seems that morphological criteria, obtained by quantitative measurement, [9 10] still furnish the most useful information on pathological changes in bones.

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Helsinki, Finland.

PEKKA VIRTAMA.

"A DEPARTURE FROM NORMAL PRACTICE"

SIR,—I am sorry Dr. Tredgold and Dr. Soddy (March 25) should write of their concern over safeguarding doctors from lonely and frustrated patients, but omit mention of their responsibility as distinguished members—indeed leaders—of the profession to safeguard lonely and frustrated patients from inexperienced, inadequately trained, and sometimes frankly psychopathic doctors. I think they would agree with me that a medical degree, an ability to hypnotise, or charming selfconfidence, per se, does not entitle a person to set up as a psychiatrist or psychotherapist. *There is a world of difference between a psychotherapist and a professional sympathiser.*

Their attempt to enlist the sympathy of general practitioners by implying that they too are at risk is specious. If a general practitioner without specialist training undertakes major abdominal surgery and things go wrong, and he does not seek expert assistance, his victim (or the dependants) deserve some compensation. Similarly a general practitioner without special training undertaking major psychiatric treatment, who does not seek expert help when difficulties arise, owes something to his victim.

They state "[The doctor] has a choice between using the [transference] relationship for the patient's benefit, or attempting to reduce it, which may entail breaking off the case." They do not mention the vitally important alternative—that the doctor through his own emotional—alas sometimes economic—need may bask in the warmth of his victim's confidence or love, perpetuating the situation and preventing the patient from going out into the world to make some sort of life for herself. The transference situation is not as unique, unknown, unpredictable, and uncontrollable as Dr. Tredgold and Dr. Soddy imply. Having suffered considerable transference difficulties in training (long letters, telephone calls, presents, invitations, visits, and intense personal interest from many patients), I know how easy it is to mismanage the transference situation, how difficult and disturbing it is to acquire training and experience in the matter.

It is a salutary thought that the untrained writer of the lyric "People will say we're in love" appears to know more of the tricks of transference than some who may have had scientific training.

How to conduct a psychotherapeutic interview has received a great deal of attention and is set out quite clearly in Colby's *Primer for Psychotherapists.*[11]

If a psychiatrist helps a woman patient on with her coat with too much alacrity, or leaps to light her cigarette, or gives her more time than specified, or goes out of his way to see her, or calls her by her Christian name, she will, understandably, think there is more in the relationship than professional

1. Greenblatt, I. J., Hartman, S. *Analyt. Chem.* 1951, **23**, 1708.
2. Virtama, P. *Acta anat.* 1957, **31**, suppl. 29.
3. Ornstein, L. *Lab. Invest.* 1952, **1**, 250.
4. Steven, G. D. *Ann. rheum. Dis.* 1947, **6**, 184.
5. Laitinen, H., Virkkunen, M., Virtama, P. *Acta rheum. scand.* 1958, **4**, 266.
6. Virtama, P. *Ann. Med. intern. Fenn.* 1960, **49**, 57.
7. Omnell, K.-Å. *Acta radiol., Stockh.* 1957, suppl. 148, 1.
8. Virtama, P. *Ann. Med. exp. Fenn.* 1960, **38**, 127.
9. Virtama, P., Mähönen, H. *Brit. J. Radiol.* 1960, **33**, 60.
10. Barnett, E., Nordin, B. E. C. *Clin. Radiol., Lond.* 1960, **11**, 166.
11. Colby, K. M. Primer for Psychotherapists. New York, 1951.

treatment or common courtesy demands. If she is wise, she will leave him quickly; if she is foolish she may not leave until her savings have gone. I do not think many doctors are guilty of these practices. Such "transference parasites" do reputable psychiatrists and the profession a great disservice.

I cannot agree with Dr. Roughton's letter (April 8), and I do not think she really believes that *genuinely* disinterested efforts to help a patient are likely to be rewarded with financial ruin.

May I end with a quotation from Spencer: "The ultimate result of shielding men [psychiatrists] from the effects of folly, is to fill the world [profession] with fools." [12]

Severalls Hospital, Colchester. RUSSELL BARTON.

MAINTENANCE OF PIPED-OXYGEN SUPPLIES

SIR,—Cylinder manifolds feeding oxygen pipelines in hospitals are all fitted with connectors adapted for coupling to cylinder valves with an outlet conforming to British Standard 341—$^{5}/_{8}$ in. (16 mm.), right-hand, female thread. This type of valve is fitted to oxygen cylinders of capacity 48 c.ft. (1·36 c.m.) and upwards, and also to cylinders in this range used for compressed air, nitrogen, helium, helium/oxygen mixtures, and oxygen/carbon-dioxide mixtures. It is thus possible, for example, for a compressed-air cylinder to be inadvertently connected to an oxygen pipe-line. Those responsible for the maintenance of piped-oxygen supplies should be reminded of this, and of the recommended code of practice for storing and handling cylinders and for cylinder identification laid down in British Standard 1319: 1955. Cylinders are painted a characteristic colour according to the colour-code shown in this standard and, of course, also bear a printed label to identify the contents.

Association of Anæsthetists of Great Britain and Ireland, London, W.C.2. H. J. V. MORTON Honorary Secretary.

STILBAMIDINE FOR TIC DOULOUREUX

SIR,—Since the letter of Dr. Smith and Dr. Miller [13] appeared, I have had experience of over 60 cases of tic douloureux followed up for three to five years.[14–16]

Stilbamidine is known to cause neuropathy of the trigeminal nerve, producing various paræsthesiae in the superficial distribution of the sensory branches. This neuropathy appears within three to five months of completing treatment; at present I give a total of 1500 mg. of stilbamidine, dissolved in glucose, in ten doses, by slow intravenous injection. I observed no drug intolerance in any patient, during or after treatment, nor any allergic reactions.

I was particularly careful in my selection of patients for treatment, because of reports of others that paresthesiæ were not well tolerated by some patients—the one drawback to treatment. I selected for treatment only the following:

(1) Patients with longstanding and severe pain over many years, with shorter and shorter spontaneous remissions.

(2) Those treated unsuccessfully by other methods, including alcohol block, and, in 3 cases, surgical section of the sensory root of the nerve as well.

(3) Older patients, not in any case younger than 40 (my patients' ages ranged from 43 to 83 years, the average being 60).

Even the 1 patient who experienced no relief—a strange case with bilateral neuralgia, already treated unsuccessfully by various operations, including prefrontal lobotomy—wanted to try a second course of the drug after six months. The other 61 patients experienced complete relief from pain, beginning three to five months after treatment was started; 7 of them so far have asked for treatment to be repeated after two to four years, when the effects on the trigeminal nerve were slowly decreasing; this was not because of renewed severe pain, but because they feared pain might recur: this is, I think, good evidence that the treatment had been well tolerated, and the paræsthesiæ as well.

Centro Cardio-Reumatologico, Arcispedale S. Maria Nuova, Reggio Emilia, Italy. PIER ANDREA MACCARINI.

12. Spencer, H. Essays, vol. III; p. 354. London, 1891.
13. Smith, G. W., Miller, J. M. *Lancet*, 1955, ii, 723.
14. Maccarini, P. A. *Policlinico, sez. prat.* 1956, **63**, 1860.
15. Maccarini, P. A. *G. Clin. med.* 1957, **38**, 5.
16. Maccarini, P. A. *Ann. Ravasini*, 1958, **41**, 10.

Obituary

VIVIAN BARTLEY GREEN-ARMYTAGE

M.D. Brist., F.R.C.P., F.R.C.S., F.R.C.O.G.

Mr. Green-Armytage, whose death we announced last week, had held a commission in the Indian Medical Service, a chair in obstetrics in Calcutta, and consultant appointments in London teaching hospitals. In each part of this triple career he won success, affection, and respect, and his varied experience in different places and among different races enhanced his contribution to the commonwealth of medicine.

He was born in 1882 at Clifton, and after qualifying from the University of Bristol in 1906 he was commissioned in the I.M.S. in the following year. In 1910 he was the Montefiore surgical medallist at the Royal Army Medical College and in 1911 he was appointed resident medical officer at the Eden and Presidency General Hospital in Calcutta. He was already taking a keen interest in midwifery and the special problems which obstetrics and gynæcological surgery presented in India, and his book, *Labour Room Clinics*, appeared in 1912. But during the 1914–18 war his work in his new-found specialty was interrupted by service in Europe, for which he was awarded the croix de chevalier of the Legion of Honour and the Serbian Order of the White Eagle.

On his return to India he resumed his work at the Eden Hospital; in 1922 he was appointed professor of obstetrics and surgeon to the Eden Hospital, and in the next years well-known books on tropical midwifery and gynæcology were published. He held his appointment at the Eden Hospital until 1933 when he retired from the I.M.S. Before he left India he was presented by some of the medical women of India with a volume of his *Selected Addresses* in gratitude for his teaching and friendship.

In 1933 he returned to this country ready and eager for a fresh start. Almost at once, by a fortunate chance, there was a vacancy at the West London Hospital and he was appointed to the staff there. Within a few years the school had become part of the University of London, and there he found scope for his gifts as a teacher. In 1936, soon after the opening of the British Postgraduate Medical School at Hammersmith, he also joined the staff there to continue his work on female infertility.

He was a fellow of the three Royal Colleges in London, but he was not unnaturally most active in the councils of the Royal College of Obstetricians and Gynæcologists, which he served as vice-president and where he endowed a travel fellowship and a lecture.

After he retired from the staff of the West London Hospital he became chairman of governors of the medical school. He also retained his busy consulting practice and was much in demand as a lecturer in medical centres both here and in distant parts of the world.

Of Green-Armytage's association with the West London, M. S. relates:

"G.A. came to the hospital in 1933. He was just due to retire from the I.M.S. when Sir Henry Simson, the hospital's gynæcological surgeon, suddenly died; and, in a letter to his great friend, Clifford White of University College Hospital,

G.A. remarked how much he would welcome such a post when he returned to England—at the relatively early age of 51. Clifford White passed the letter to Oswald Addison, then senior surgeon and chairman of the medical committee at the West London. It so happened that Simson's death was immediately followed by the loss both of the assistant surgeon and the registrar, so that the hospital found itself with no staff at all in the gynæcological department. Under these circumstances Addison considered it appropriate to communicate the contents of Clifford White's letter to the medical committee which, after a fairly long discussion, recommended that G.A. be appointed to the vacant senior post. Not unnaturally there were members of the staff who were reluctant to recommend the appointment of a colleague they had never seen. His professional reputation stood high, but he had been somewhat of a legendary figure ever since (and, indeed, during) his student days at Bristol, and many stories had circulated about him, especially in connection with his war-time activities in what was then called the Near East. If he thought a line of action was right, he fought for it selflessly and usually got his way even though it meant a battle with his superior officers, who must often have found the young and energetic captain rather a thorn in their flesh. But the decision to invite him to join the West London staff was unanimous and the invitation was promptly accepted.

"G.A. will long be remembered as a dynamic and successful teacher. His methods were unorthodox. Chalk and blackboard not being provided in his outpatient clinic, he substituted soap and window for his illustrations. He was inclined to be dogmatic, which undergraduates like, and, if his teaching was rather individual, his epigrammatic utterances impressed themselves on his hearers. It would sometimes happen that one of his students would produce one of his unorthodoxies at a clinical or viva-voce examination; the examiner would exclaim, 'Whoever taught you *that*?', knowing of course perfectly well the origin of the view expressed but unable to resist the temptation to pull the leg of a colleague even at the expense of a nervous candidate.

"Any qualms that members of the West London staff may have entertained at introducing so powerful a personality into the hospital community were soon dispelled. G.A. proved himself a delightful and charming colleague and took a most active part in the professional, administrative, and social life of the hospital. His gift of eloquence ensured his popularity in the medical school, and he was often called on to exercise his gift as an after-dinner speaker of unusual charm and wit. Both his colleagues and old students will look back with gratitude to their association with one who gave such distinguished service to his specialty and to medical education. He deservedly has a world-wide reputation and his loss will be felt by colleagues and patients in many lands, but nowhere more than in the school and hospital which he served so faithfully during the later years of his life."

J. C. McC. B. writes:

"Green-Armytage's name and magical reputation attracted to him patients and students from many countries. To postgraduates visiting Hammersmith during the war, and to those, like myself, returning at the end of the war after a long absence, he was unfailingly helpful and kind, and many a gynæcologist both in this country and abroad owes much to him. In his very specialised field of tubal plastic surgery he was pre-eminent, performing the most intricate operations with a delicacy of touch and finesse which was a joy to behold. Each new technical advance was carefully recorded by the camera, and he has left behind him a remarkable collection of films illustrating his techniques. His reputation was such that he was continually invited to lecture and demonstrate his operative methods in all parts of the world. His vitality was astounding and until the day he entered hospital three weeks ago he was constantly striving to develop new techniques, and always ready to adopt novel methods if they seemed promising. In consequence his teaching was progressive, vigorous, and stimulating.

"In a wider sense he was extremely interested in the problems of medicine within the Commonwealth, and he used all his wisdom and influence to help men and women from the Commonwealth in their quest for training. Postgraduate students from all over the world, and especially from India, the land he knew so well, have cause to be grateful to him for the kindliness and understanding with which he met their problems, and without a doubt in his world-wide travels he was one of the great ambassadors of British medicine. G.A. died as he would have wished to die, vigorous and active until the last. There cannot be one person who knew him who will fail to mourn the passing of such a man."

DENIS GEORGE KENNEDY

B.A., M.B. Dubl., D.P.M.

Dr. Denis Kennedy, medical superintendent of Lingfield Hospital School for Epileptic Children, died on April 4 at the age of 55.

He was born and educated in Dublin, and he graduated B.A. from Trinity College in 1928 and M.B. in 1931. He held posts in the Royal City of Dublin, the Drumcondra, and the Rotunda Hospitals, before coming to England in the mid-thirties, where he held posts as assistant medical officer at the County Mental Hospital, Northampton, and as assistant medical officer and pathologist at Fulbourn Mental Hospital, Cambridge. He joined the R.A.M.C. early in the late war, and directed a blood-transfusion unit before becoming a psychiatric specialist with the rank of major. He obtained the D.P.M. in 1942. He served in the North African and Italian campaigns and after his return from abroad was area psychiatrist for Northern Command. In 1946 he was demobilised and soon afterwards was appointed medical superintendent of Lingfield Epileptic Colony, which, in 1957, became Lingfield Hospital School for Epileptic Children. He served on the committee of the Association of Independent Hospitals (of which he had been chairman), the F.S.S.N., and the local youth employment service.

P. K. A. McW. writes:

"The change of name at Lingfield from 'colony' to 'hospital school' accompanied a radical change of policy, and Dr. Kennedy will be remembered best of all for his pioneer work in this connection. Replacing the then universally accepted policy of the custodial care of epileptic children by the idea of rehabilitation, he discharged them, when their seizures were controlled, to their parents and appropriate local schools. After five years this policy, which has enabled many epileptic children to be reintegrated into the community, is now firmly established. Nearly half the children admitted to Lingfield are rehabilitated in this way, and the average length of stay of a child is now between two and three years.

"During his term of office, many material improvements also took place. Five new homes were built and the process of modernising the older homes is nearing completion. There is a fine new hostel for resident staff, and the new school, opened in 1957, is modern and well equipped. The children wear an attractive school uniform, have normal school holidays, and take part in a wide range of extracurricular activities. A few months ago an E.E.G. machine was installed as the first step towards establishing an investigation centre, for Dr. Kennedy was ever conscious of the urgent need for research into childhood epilepsy.

"Denis Kennedy was humble, humane, sincere, and charming. He had a wide circle of friends and was always

ready to come to the aid of all who sought his assistance. His ability for clear reasoning, sound judgment, and eagerness to render necessary practical help were outstandingly obvious. He had a profound love of children, especially the handicapped, and his colleagues knew the extent of his concern for the well-being of the 400 children at Lingfield (to whom he referred as 'the kids') and for their parents. His personal letters to the parents of his patients revealed the depth of his understanding of their problems. His interests were wide and his hobbies varied. He was one of the first men in Dublin to have an amateur radio-transmitting licence; he was an accomplished engineer, a keen photographer, and an ardent caravanner.

"It is natural to regard the new and improved buildings and the modern facilities at Lingfield as Denis Kennedy's memorial, but perhaps an even greater, though less tangible, memorial is the happiness afforded to a vast number of children who, as a result of his work, are now leading happy and useful lives."

In 1944 Dr. Kennedy married Miss Rita Vere, who survives him.

JULES BORDET

M.D. Brux.

IF Professor Bordet had died forty years ago, it would have been correct to say that his death signalised the passing of an era; but he, alone among many, survived long after that era had come to an end. He was one of the band of European workers who created the science of immunology. Taking over from their forebears the crude experience of vaccination, they studied not only the mechanism that underlay the resistance of the body to disease but also the far wider phenomenon of the reaction of living tissue to foreign substances. Metchnikoff, Buchner, von Behring, Richard Pfeiffer, Ehrlich, Nuttall, and Bordet, to name only some of the principals, toiled and strove and fought to establish the fundamental laws of immunity. So successful were they that within a period of a little over ten years, between 1890 and 1901, all the major reactions on which our present serological technique is based were discovered. It was a period of triumphant activity, analogous to the period of bacteriological discovery in the '70s and '80s, and in it Jules Bordet played one of the leading parts.

At the age of twenty-five he published his study of the properties of a bacteriolytic antiserum, showing that in its interaction with the bacillus two separate substances took part—one thermolabile and unaffected by the process of immunisation, the other thermostable and greatly increased by immunisation. Three years later he found that the same mechanism held for the lysis of red-blood corpuscles by an antiserum. Along with Gengou he introduced in 1901 an indirect method for detecting the absorption of the thermolabile element (complement) by sensitised bacteria. This depended on the simple observation of the lysis of red-blood corpuscles in place of the more difficult microscopical demonstration of bacterial lysis. The complement-fixation test, as it came to be called, was found to be applicable to all the various antigen-antibody reactions in which complement was concerned. It formed the basis of the Wassermann reaction, and is now one of the most widely used tools in bacteriology and virology. With the study of the conglutination reaction in 1909, Bordet's work on serology was virtually complete.

In his attempt to explain the phenomena that he had observed, on the basis of adsorption by colloids, Bordet came into conflict with Ehrlich, who regarded the antigen-antibody reaction more in the nature of a firm chemical union. This is not the place to review the controversy. As subsequent work has shown, both views were partly correct, and the discrepancy between them has now been largely resolved. In the whole dispute, however, Bordet was actuated by the spirit of a genuine seeker after truth, putting forward his explanations with great modesty and affording an example in behaviour to all experts who find themselves in disagreement with each other.

Jules Jean Baptiste Vincent Bordet was born in 1870 at Soignies in Belgium. His university education was in Brussels. He studied at the Institut Pasteur in Paris from 1894 to 1901, and then returned to Brussels to found an Institut Pasteur, where he remained for the rest of his working life. In 1906 he published with his collaborator Gengou an account of the cultivation and properties of the whooping-cough bacillus, and in 1910 he published his observations on the organism of pleuropneumonia, which confirmed those of Nocard. From 1907 he was professor of bacteriology in the University at Brussels. He was elected a foreign member of the Royal Society in 1916, and awarded in 1919 the Nobel prize in the section of physiology and medicine. He died on April 6 at his home at Ixelles at the age of 90.

Bordet's main contributions were made in the short space of twenty years while he was still a young man, but he lived to see the application of his discoveries to a more extensive field than he could ever have visualised. He was a great scientist; he will be affectionately remembered by those who had met him; and he will rank among the immortals.

G. S. W.

Dr. S. HOWARD ARMSTRONG

N. H. M. writes:

"I knew Howie in those golden years at Harvard and we had kept in touch ever since. To give the texture of the man, may I recall two happy memories? The first, a party in his home in Boston 48 hours after I had arrived. Such was the diversity of his friends and the splendour of his hospitality that it seemed to me, as night merged into morning, that he must know everyone in the United States and that they were all there, crammed into the house. The second, a lovely day in Boston, playing hookey with Howie from Cohn's laboratory—a feat in itself. Together we completed a magnificently incompetent round of golf at the Brookline country club, fortifying ourselves from hole to hole as required, and returning to the laboratory at 10 P.M. to work, and work hard, till dawn the next day.

"In these two vignettes are something of his spontaneous kindness to a stranger, wonderful eccentric companionship, and almost obsessive dedication to science in the service of medicine. He was a splendid friend."

Appointments

EDWARDS, J. W. L., M.D. Lpool, M.R.C.P.: part-time consultant physician in allergy, Liverpool Chest Hospital.

FINN, O. A., M.D. Glasg.: consultant dermatologist, Stirling, Falkirk, and Alloa area hospitals and Stobhill Hospital, Glasgow.

GROSSART, K. W. M., M.B. Glasg., D.M.R.D.: consultant radiologist, Southern General and associated hospitals, Glasgow, with duties in the neuro-surgical unit at Killearn Hospital.

HARRISON, A. R., M.D. Lond., M.R.C.P.: part-time consultant physician, St. Peter's, St. Paul's, and St. Phillip's Hospitals, London.

LITTLEWOOD, A. H. M., M.B. Cantab., F.R.C.S.: consultant plastic surgeon, Whiston, Alder Hey Children's, and Leasowe Hospitals.

LLOYD-DAVIES, D. G., F.R.C.S.E., D.L.O.: consultant E.N.T. surgeon, North Devon Infirmary, Barnstaple.

MCKENNA, W. B., M.D. Glasg.: consultant dermatologist, Southern General Hospital and Western Infirmary, Glasgow.

East Anglian Regional Hospital Board:

EVANS, E., M.B., D.C.H.: registrar in psychiatry, Suffolk mental hospitals.

EVANS, T. A., M.B. Lond.: surgical registrar (casualty), Ipswich and East Suffolk Hospital.

JHA, P. N., M.B. Patna, D.T.M. & H.: registrar in geriatrics, West Suffolk hospital group.

KELLY, M. G. C., M.B. Dubl.: registrar in psychiatry, Little Plumstead hospital group.

LAMPLUGH, CATHERINE M., M.B. Leeds, D.OBST.: registrar in obstetrics and gynæcology, Peterborough hospital group.

Notes and News

HOSPITAL INPATIENT STATISTICS

REPORTS on the Hospital Inpatient Inquiry from 1958 onwards are appearing in two parts—a brief part I containing advance information, followed by part II with tables and commentary. Part I for 1958 appeared last May [2] and part I for 1959 is expected shortly. Meanwhile the full report for 1956 and 1957 has come out this week.[1]

Information for the inquiry is supplied by hospitals, which complete a form for one patient in every ten discharged, giving a confidential summary of the case-record. Since 1958, virtually all hospitals (except psychiatric) in England and Wales have taken part; but in 1956 and 1957 the coverage was less complete.

In hospitals relevant to the inquiry there were 3,485,000 discharges and deaths in 1957. The average duration of each spell of hospital care was 22 days for males and 20 for females—a slight reduction on the two previous years. Maternity cases stayed an average of 10 days after delivery in 1957, compared with 11 days in 1955, and the proportion of mothers discharged within 7 days of delivery increased from 7% in 1955 to 13% in 1957. In "acute" non-teaching hospitals the average length of stay was shortest in medium-sized hospitals.

From data on duration of stay, the number of hospital beds used by different groups of patients can be calculated. The number of beds required per 10,000 population ranges, for males, from 20·8 at ages 15–24 to 188·8 at ages 75 and over, and for females from 18·7 at ages 5–14 to 187·3 at 75 and over.

University of London

Dr. P. Armitage, a member of the Statistical Research Unit of the Medical Research Council at the London School of Hygiene and Tropical Medicine, has been appointed to the chair of medical statistics at the school, and Dr. Dennis Lacy, lecturer at St. Bartholomew's Hospital Medical College, to the readership in zoology and comparative anatomy at the college.

University of Birmingham

The title of senior clinical tutor in pædiatrics and child health has been conferred on Dr. J. S. Oldham, pædiatrician to Dudley Road Hospital. Dr. J. H. Edwards has been appointed lecturer in the department of social medicine.

University of Wales

On July 21 the honorary degree of D.SC. will be conferred on Dr. William Evans and of LL.D. on Mr. H. Morriston Davies.

Queen's University, Belfast

Sir Frank Montgomery, honorary consulting radiologist to the Royal Victoria Hospital, Belfast, has been re-elected pro-chancellor.

Royal College of Surgeons of England

At a meeting of the council on April 13, with Sir Arthur Porritt, the president, in the chair, Mr. W. J. Dempster, F.R.C.S.E., and Mr. O. D. Morris, F.R.C.S.E., were admitted to the fellowship *ad eundem*.

The Jacksonian prize was awarded to Mr. C. R. Helsby, and the Cartwright prize to Mr. G. L. Howe. Dr. M. S. Israel was appointed lecturer in microbiology in the department of pathology. The following were elected fellows without examination as medical practitioners of twenty years' standing:

Dr. R. A. S. Cory, Dr. E. R. Williams, Sir Wilfred Fish, Prof. R. A. Willis, Dr. L. Guttmann, Group-Captain A. L. Knipe.

A diploma of fellowship was granted to J. W. Fisher, and the following diplomas were granted jointly with the Royal College of Physicians:

D.O.—Adeeb Saleeb, Somasundaram Anandarajan, J. R. S. Barton, John Beaumont-Haynes, Shirley D. Campbell, Anthony Carroll, A. F. M. Abdul Alim Chaudhury, Chin Mee Hong, I. A. Chisholm, Abdul Matin Chowdhury, Costas Costa Constantinides, A. W. Craig, Pritam Dhir, W. H. G. Douglas, Mohammad Erami, H. B. Fraser, R. E. R. Gillespie, Chandra Prakash Gupta, R. D. Hunter, Ghazi Jamil Hussain, Aminul Islam, Ramesh Chandra Jaiswal, O. A. H. Johnson, Nurul Alam Khan, Ko Lay, Usama Majzoub, Maung Myint Thein, Mujtaba Ali Mirza, F. P. Morris, Ajit Kumar Mukherjee, C. J. Must, Mya Han, J. O. Odulate, Donald Parker, Nisar Ahmed Pathan, Barend Tevere Pienaar, P. V. Pigott, R. M. Powrie, Salunkay Gopalrao Ram Narayan Rao, Samir Nessim Morcos Rizk, Muriel E. Rolfe, Diptish Roychowdhury, D. W. Sabiston, J. P. Sarks, Nanak Chand Singhal, D. M. Somerville, Kathleen M. Thomas, C. O. Thompson, Pamela M. Thorne, Badri Narayan Tiwari, Syed Abdul Wadud, P. H. Williams, Shamsi Mohammed Yahya, Abdel Hafiz Abu Yousif.

D.M.R.D.—D. H. Abbott, J. C. Anderson, L. E. Apikian, O. P. Charlton, F. L. Cole, Peter Dutton, R. H. Gibbon, J. N. Glanville, Zvonimir Grahovac, D. C. Jackson, Ian Kelsey Fry, R. T. McKay, John Mitchell, Narendrakumar Laxmidas Patel, Sabah Hanna Petros, Joachim Mathias Pinto, J. L. Price, M. D. Rawson, S. P. Smith, Paul Sneider, I. D. Thompson, Mahasena Banda Wærakaulle.

D.M.R.T.—C. D. Collins, G. J. A. Edelstyn, J. I. Gold, F. A. L. Kircher, Edna Matthews, E. R. Monypenny, E. A. Ramanayake, Priscilla A. Ridge, Margery Williams.

D.C.H.—Iftikhar Ahmed, Abdul-Rahman Ahmad Akta, A. J. R. Anderson, Anjorin Animashaun, Judith M. Babb, D. B. Bannerjee, Winifred M. Bartindale, Kenneth Bass, G. J. Biggam, J. A. Brown, Doreen R. G. Browne, M. P. Buckley, Hilda D. Bune, Sami Bunni, Aleyamma Kollamparampil Chacko, Kim Yong Chan, Brenda M. Chant, N. A. Coutts, Arun Sekhar Day, R. B. Deering, Ann C. Deuchar, J. A. Dodge, Elizabeth Duane, Iris M. Duke, Angela K. Earls, Abdel-Hamid Mohamed El-Shaboury, Beryl H. Evans, F. F. Fenech, M. T. Fernandes, R. M. A. Fernando, Jean M. Firth, C. E. Forbes, Anna L. Frenkiel, G. B. Gasson, G. S. Gilchrist, Gay J. Gillibrand, B. P. Glaun, C. B. T. Grant, Radha Charan Gupta, Ram Chandra Gupta, Shyam Prakash Gupta, J. R. Harper, J. T. Harries, Mohammad Zahirul Hasan, Gerald Hass, G. G. Hay, Jean Hellings, G. G. Hinton, Vijaya Lakshmi Hooja, T. W. Hoskins, Jamil Menashi Ibrahim, Sylvia Ingold, Tit Shing Ip, Susantha Jayaratne, Sumithra Jayaweera, Gnanasekeram Jeganathan, Rosemary A. Johnson, Jocelyne D. L. Kane-Berman, Edathil Keloth Karunakaran, Rena D. Katz, K. M. Kewalramani, H. R. G. Lennox, Yusufu Lutwama, Madan Singh Madan, Dilip Mahalanabis, Kirpal Singh Mankoo, John Martin, Moira S. Meldrum, C. G. Miller, Agnes M. Mills, June Mills, A. R. L. Neil, Wing Hang Ng, Ochiabuto Christian Nwankwo, K. M. Parry, Kantibhai Chaturbhai Patel, Wai-On Phoon, Lizette G. Potts, Mohammed Qadeerullah Qureshi, Barabra J. Rashbass, Sylvia J. A. Raymond, E. O. R. Reynolds, Naomi S. Richman, Mary S. Rizk, E. U. Rosen, E. J. R. Rossiter, K. W. Rowden, Hermione B. Roxburgh, S. S. Sanders, Gloria H. Sands, Imdadali Badruddin Sardharwalla, R. S. C. Scoular, Khin-Khin Sein, C. A. Selway, W. G. Shakespeare, Sahib Kadhum Shammaa, Mukhtar Khaled Sharif, Syed Hosain Shirazee, Swadesh Sikka, Walter Sharwan Anandpati Singh, Clare N. Smith, Jacqueline A. K. Smith, Pramuan Sunakorn, Gaius Backholer Sutton, Adikanda Swain, Nyamatmiyan Akbarmiyan Syed, Reni Wiiu Tents, Kathiravelu Thirumavukkarasu, Ena E. Thomas, J. G. Thomas, N. E. Thomas, W. M. S. Thomson, Rita C. Travers, Yen-Chow Tsao, Jill P. Wayland, B. S. Wilson, Marie B. Wilson, Susan E. J. Young, Husein Ali Zarnegar.

D.P.M.—H. D. Adler, Norma A. Beardwell, M. I. Bruk, R. A. Flood, E. N. Glick, Ma Mya Sein.

D.T.M. & H.—C. D. Addo, Suraj Prakash Ahuja, Om Prakash Arya, E. S. W. Bidwell, N. A. Boyd, R. S. Britton, Beatrice M. Brown, A. D. M. Bryceson, A. W. Burdon, Mukhtar Ahmad Chishti, E. W. Dade, Bhagabat Charan Das, I. A. A. De Coutere, Carpo De Silva, Sivaguru Dharmavartha, Hamadnalla Elamin, R. W. Emmons, Zoheir Sayed Farid, A. K. Foli, C. W. Free, C. J. Garrett, John Gray, Lars Magnus Hambraeus, Subhi Hannoudi, Sadrudin Alibhai Janmohamed, M. L. Johnson, W. G. Johnston, J. B. Kelly, Rana Sultan Ahmad Khan, Pran Nath Kochhar, Ateeque Ahmed Khawaja, Jarno Jouko Uolevi Laine, M. I. Lander, Ronald Marks, Syed Fazleali Meerza, R. J. Moylan-Jones, M. G. O. Parrish, Nisar Ahmed Pathan, P. B. Pickles, C. R. M. Prentice, Mohummad Raza, Syed Amir Sajjad Rizvi, R. D. C. Southcott, J. H. Taylor, J. L. E. W. Thomas, G. W. Thompson, A. D. Whanger.

Faculty of Anæsthetists.—Prof. W. W. Mushin has been elected as dean and Dr. H. J. V. Morton re-elected as vice-dean. The following have been elected fellows without examination:

Prof. M. S. el Hakeem, Dr. C. S. Hones, Dr. L. H. Lerman, Dr. O. I. E. Nicholson, Dr. V. Rajagopalan.

A diploma of fellowship has been granted to J. W. Lloyd.

Royal Faculty of Physicians and Surgeons of Glasgow

At a meeting on April 10, with Dr. J. H. Wright, the president, in the chair, the following were admitted to the fellowship:

Muhommad Azim Almani, Mohammad Aslam, Mohamed Abdul Qayum Faiz, J. M. Macfie, Peter McKenzie, Mangalore Kesava Pai, S. D. S. Park, Ramdath Ramkissoon, Rameshchandra Hiralal Shah, J. A. Thomson, Christopher Gunapala Uragoda, Quazi Abul Mansur Mahbubuzzaman Zaman, *qua physician;* William Christian Brown, Bishnu Ram Das, Adegboyega Adebowale Efunkoya, Fouad Hassan Ghali, Munir Ahmed Siddiqui, A. C. Smith, *qua surgeon.*

Royal College of Physicians of Ireland

The following were successful in a recent examination for the diploma in obstetrics:

I. E. E. A. Aboul-Magd, E. J. T. Giblin, R. W. J. R. James, K. T. Maphathe, A. Meade, H. B. Miller, R. Omar, A. A. Shaikh, S. Sulochana, J. P. Walsh.

London County Council

The following doctors have been elected to the L.C.C.: Dr. I. N. Samuel, Dr. Harry Rezler, Mr. E. H. T. Hambly, Dr. D. T. Pitt, Dr. D. L. Kerr, Dr. G. F. Vaughan.

1. Report on Hospital Inpatient Inquiry for the two years 1956 and 1957. 1961. H.M. Stationery Office. Pp. 335. 18s.
2. Report on Hospital Inpatient Inquiry for the year 1958, part I, preliminary tables. 1960. H.M. Stationery Office.

Health Education

Cooperation in health education by local health authorities in the south-east of England is to be promoted by the formation of a Home Counties coordinating committee. With Dr. Denis Pirrie as chairman, this committee will consist of medical officers of health or their representatives and Dr. A. J. Dalzell-Ward, the medical director of the Central Council for Health Education. At their recent meeting at County Hall it was agreed that a poliomyelitis publicity campaign should be organised for the autumn. The main effort will be directed towards securing publicity at public-houses and railway stations, and this will be supplemented by local publicity at welfare centres, shops, and so on. By these means, it is hoped, people with whom little or no direct contact is made through the local-authority health services will be reached at places to which they resort.

Professor Leiper's 80th Birthday

April 17 saw a large assembly of the profession, with secretaries and technical assistants, gathered at the London School of Hygiene and Tropical Medicine to celebrate the 80th birthday of Prof. R. T. Leiper, F.R.S., when he was presented by Sir William MacArthur with a memorial volume of the *Journal of Helminthology*, which he originally founded. This supplement contains 137 signatures of admirers in all parts of the world, followed by tributes from his closest associates and a series of technical articles by pupils and fellow helminthologists. At the ceremony he was presented by Dr. Weindel, of the German Embassy, with the Bernhard Nocht medal bestowed on him by the tropical institute of Hamburg. A reception was afterwards held in the common-room by Prof. George Macdonald, the acting dean, at which Dr. Elsie Toms, the mayor of St. Albans, spoke appreciatively of Professor Leiper's public work as justice of the peace in that city.

Bequests

Lady Teale, widow of Sir Francis Teale, has left one-fifth of the residue of her £66,000 estate to the Royal College of Physicians of London to endow a biennial lecture on diseases of children, two-fifths to the "Cancer Research Fund", and two-fifths to University College Hospital Medical School for research in the department of clinical medicine.

Bequests made by the late Dr. J. F. Brailsford, who left £41,000 gross, include £1000 to the University of Birmingham to endow a James Brailsford prize for the most promising student in radiology at the medical school.

Royal Photographic Society

The combined Royal Colleges bronze medal has been awarded to Dr. David Ruhe, associate professor of public health at Kansas University Medical School, for two films on emergency airways for cricothyroid puncture and tracheotomy. Entries for the 1961 award should be sent to the hon. secretary of the medical group, 16, Princes Gate, London, S.W.7, by Sept. 30.

Manchester Foot Hospital and School of Chiropody

A new chiropodial appliance department at this hospital and school, which forms part of the United Manchester Hospitals, was opened by Sir Harry Platt on April 13. It consists of five main rooms, with waiting-room and office, and includes a plaster room where the 28 students in the school will be taught the many varying casting techniques.

On Wednesday, April 26, at 11.30 A.M., at the Whittington Hospital Archway Wing, London, N.19, Prof. Alan Kekwick will give a lecture on obesity.

At a meeting of the South East Metropolitan Regional Tuberculosis Society to be held on Saturday, April 29, at 11 A.M., at Preston Hall Chest Hospital, Aylesford, Kent, Prof. F. R. G. Heaf and Dr. D. L. Pugh will speak on the eradication of tuberculosis.

A meeting of the Biochemical Society is to be held on Friday and Saturday, April 28 and 29, at the University of Birmingham, and will begin at 2 P.M. on Friday with a colloquium on metabolic pathways of foreign compounds.

At a meeting of the Belmont Hospital Clinical Society on Thursday, April 27, at 8 P.M., Miss I. E. B. Menzies will speak on nurses under stress.

Mr. B. A. McSwiney will take up the appointment of clerk of the governors of St. Thomas's Hospital at the end of the year.

Mr. William Dempster left on April 16 for a two-week British Council working visit to Hungary at the invitation of the Hungarian Academy of Sciences. During his stay he will demonstrate the new technique of kidney transplanting.

CORRIGENDUM: *Prevention of Hospital Infection.*—Our leader of March 18, in mentioning some of the people who have done fundamental work on the streptococcus, gave the wrong Christian name to Frederick Griffith, who differentiated the hæmolytic streptococci by agglutination. With his friend and fellow bacteriologist at the Ministry of Health, W. M. Scott, Dr. Griffith was killed by enemy action in 1941.

Diary of the Week

Monday, 24th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. Mr. F. W. Southwood: Villous Tumours of the Large Intestine—their Pathogenesis, Symptomatology, Diagnosis, and Management. (Hunterian lecture.)

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5.30 P.M. *Odontology.* Mr. Lester R. Cahn (New York): Early Detection of Oral Cancer—the Dental Surgeon's Responsibility.

MANCHESTER MEDICAL SOCIETY
9 P.M. (Medical School, University of Manchester.) *General Practice.* Lord Taylor of Harlow: Harlow Experiment.

Tuesday, 25th

RUSCOE CLARK LECTURE
6 P.M. (Royal College of Surgeons of England.) Sir Harry Platt: Care of the Injured.

ST. MARY'S HOSPITAL MEDICAL SCHOOL, W.2
5 P.M. (Wright-Fleming Institute.) Dr. Louis Steingold: Anæmia of Pregnancy.

ROYAL STATISTICAL SOCIETY
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) *Medical Section.* Dr. Yves Biraud: Present Trends in International Health Statistics.

Wednesday, 26th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P.M. Prof. David Slome: Physiology of the Vestibular Apparatus. (Arnott demonstration.)

POSTGRADUATE MEDICAL SCHOOL OF LONDON: Ducane Road, W.12
2 P.M. Sir Roy Cameron: Nutmeg Liver.

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Dr. Jack Pepys: Mechanisms of Hypersensitivity in Pulmonary Disease.

BRITISH INSTITUTE OF RADIOLOGY
8.30 P.M. (Church House, Westminster, S.W.1.) Sir Bernard Lovell: Conditions of Outer Space. (Silvanus Thompson lecture.)

UNIVERSITY OF OXFORD
5 P.M. (Radcliffe Infirmary, Oxford.) Dr. Ida Mann: Research on Eye Disease among Australasian Aboriginal Tribes. (Litchfield lecture.)

Thursday, 27th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
4 P.M. Prof. W. G. Penfield: The Brain's Record of Experience. (Lister oration.)

UNIVERSITY OF LONDON
5.15 P.M. (London School of Hygiene and Tropical Medicine.) Prof. F. Lynen (Munich): Biological Pathways to the Carbon Skeleton in Natural Products. (First of three lectures.)
5.30 P.M. (School of Pharmacy, 29, Brunswick Square, W.C.1.) Prof. A. Brodal (Oslo): Lateral Vestibular Nuclei of Deiters and its Connections—an Example of Somatotopical Organisation in the Central Nervous System.

POSTGRADUATE MEDICAL SCHOOL OF LONDON
4 P.M. Dr. R. E. Bonham-Carter: Results of Cardiac Surgery under One Year of Age.

ROYAL SOCIETY OF MEDICINE
8 P.M. *Urology.* Mr. N. L. Shepperd, Dr. A. H. Grace: Prostatectomy under Hypotensive Anæsthesia.

LONDON JEWISH HOSPITAL MEDICAL SOCIETY
8.15 P.M. (11, Chandos Street, W.1.) Dr. Edward Glover: Behaviour Disorders as Illness.

HONYMAN GILLESPIE LECTURE
5 P.M. (University New Buildings, Teviot Place, Edinburgh.) Mr. I. Simson Hall: Functional Surgery of the Ear.

UNIVERSITY OF ST. ANDREWS
5 P.M. (Physiology Department, Queen's College, Dundee.) Dr. Paul Fourman: Parathyroids.

Friday, 28th

POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M. Mr. R. T. Turner-Warwick: Lymphatics in Breast Cancer.

ROYAL SOCIETY OF MEDICINE
5 P.M. *Pædiatrics.* Dr. N. R. Butler, Dr. A. E. Claireaux, Mr. R. G. Law, Mr. D. G. Bonham, Dr. M. J. Dawkins: Perinatal Mortality Survey under the auspices of the National Birthday Trust Fund.
8.15 P.M. *Obstetrics and Gynæcology.* Prof. T. N. A. Jeffcoate, Prof. W. M. Davidson, Prof. A. C. Stevenson, Prof. P. E. Polani: Chromosome Abnormalities and Nuclear Sexing.

INSTITUTE OF CHILD HEALTH, The Hospital for Sick Children, Great Ormond Street, W.C.1
5 P.M. Dr. C. H. M. Walker (University of Colorado): Partial Perfusion in Puppies of Premature Weight.

SOCIETY OF APOTHECARIES OF LONDON, Blackfriars Lane, E.C.4
5 P.M. *Faculty of the History of Medicine and Pharmacy.* Sir Geoffrey Keynes: Timothy Bright. (Gideon de Laune lecture.)